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FREQUENCY AND SIGNIFICANCE OF HEPATIC EDEMA

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Edema of the hepatic parenchyma, characterized by a collection of fluid between the liver cell cords and the walls of the sinusoids, although familiar to every pathologist, has so far not been considered of great significance. Mechanical factors, such as stasis, as well as inflammatory conditions of the liver have been regarded as causes (Orth [1]). The focal flecking of the liver in sepsis, first described by Helly,[2] is due to focal edema, which points to general toxemia as another probable factor. Hepatic parenchymal edema has generally been regarded as merely secondary to a primary process of real significance. For years, Roessle [3] alone has looked on hepatic edema as the evidence of a toxic lesion of the capillary wall, which becomes permeable to plasma and suffers destruction and desquamation of its endothelium. In the course of its regeneration collagen fibers develop within or on the capillary wall. Thus, "a cirrhotic process is initiated by alterations of the vascular wall and toxic edema." Roessle [4] has more recently maintained that parenchymal toxic edema of the liver is equivalent to an acute diffuse serous hepatitis and has stressed its importance in the pathogenesis of atrophic cirrhosis of the liver and the liver changes in exophthalmic goiter.[5] In logical sequence Roessle has extended his concept of serous inflammation to other organs. He discusses its significance in general pathology and in the pathogenesis of many sclerosing processes which have not

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1. Orth, J.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, A. Hirschwald, 1887, vol. 1, p. 919.

2. Helly, K.: Verhandl. d. deutsch. path. Gesellsch. **13**:312, 1909.

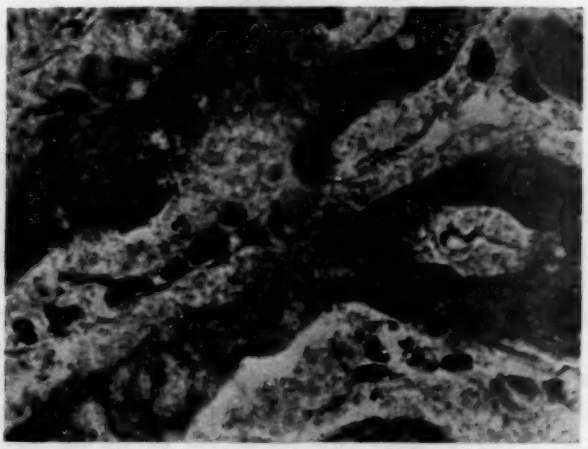
3. Roessle, R.: Virchows Arch. f. path. Anat. **188**:484, 1907.

4. Roessle, R.: Entzündungen der Leber, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, no. 1, p. 250.

5. Roessle, R.: Virchows Arch. f. path. Anat. **291**:1, 1933.

thus far been understood.[6] Eppinger, Kaunitz and Popper[7] have not only accepted the concept of Roessle but have attempted to apply it in the explanation of the mechanism of a great variety of morbid processes. It is not within the scope of this communication to review in detail the far reaching conclusions of Eppinger and his co-workers as stated in their recently published monograph.

The observations and inferences of Roessle and Eppinger seemed of sufficient importance to warrant investigation. In our studies of hepatic parenchymal edema we have attempted to establish (1) the frequency of its occurrence in a group of unselected cases, (2) its relative frequency in various diseases and (3) its association with other local or general pathologic alterations.



Section of liver from a patient who died of mercury bichloride poisoning. The pericapillary spaces are distended and filled with granular (protein) material. The capillaries are compressed.

MATERIAL AND METHODS

In order to determine the incidence of intralobular hepatic edema, an initial series of sections of liver obtained in 505 consecutive autopsies was studied (table 1). We regarded as showing edema only those sections in which the capillary walls were separated from the liver cell cords and in which the distended pericapillary spaces (Disse spaces) contained stained granular (protein) material (figure). Mere separation of the capillary wall was not accepted as evidence of edema, since focal detachment alone could be demonstrated in almost every instance, and even widespread detachment very frequently. This separation can also be accentuated by fixatives, especially alcohol. Boiling of the blocks of liver prior to fixation in solution of formaldehyde U. S. P. did not demonstrate protein in the Disse spaces more conspicuously. Having convinced ourselves that fixation in Zenker's solution or boiling in saline solution before fixation in solution of

6. Roessle, R.: Klin. Wchnschr. **14**:769, 1935.

7. Eppinger, H.; Kaunitz, H., and Popper, H.: Die seröse Entzündung. Vienna, Julius Springer, 1935.

formaldehyde produced no picture different from that following fixation in 20 per cent neutral solution of formaldehyde, we subsequently employed only the latter. Special staining methods were applied. Mallory's aniline blue fuchsin stain revealed very sharp contrasts between the capillary wall and the granular staining protein. A deep eosin hematoxylin stain was, however, sufficiently satisfactory. As control material, we obtained, through the courtesy of the Medical Examiner's Office of the City of New York, blocks of liver from thirty normal persons who had died suddenly from violence.

In a second series we examined selected groups of cases (table 2). The selection was made either because the group had shown frequent edema or because

TABLE 1.—*Results of Examination of Liver for Parenchymal Edema in Five Hundred and Five Unselected Cases*

Cause of Death	Total Number of Cases	Number in Which Hepatic Edema Was Found	Comment
Cardiac insufficiency			
Rheumatic fever	34	10	
Acute coronary occlusion	24	10	
Old coronary occlusion	8	3	
Cardiac hypertrophy with disseminated fibrosis	11	7	
Pulmonary embolism	14	5	
Glomerulonephritis			
Acute	3	3	
Subacute	3	3	
Chronic	4	1	
Malignant nephrosclerosis	11	7	
Uremia other than that due to nephritis	21	8	Polycystic kidneys, 3; pyelonephritis, 4; carcinoma of bladder, 1
Infectious diseases			
Lobar pneumonia	14	1	
Bronchopneumonia	61	3	
Influenza	5	4	
Sepsis (bacteremia)	21	4	
Subacute bacterial endocarditis	8	0	
Peritonitis	54	0	
Status asthmaticus	2	2	
Malignant tumors of other organs	35	0	
Leukemia	9	0	
Miscellaneous	163	8	
Death from anesthesia	2	2	
Suicide by strangulation	1	1	
Aplastic anemia	2	1	
Lymphosarcomatosis	2	1	
Disseminated tuberculosis	19	2	
Fibroma of pleura	1	1	
	505	79 (15 per cent)	

the statements of previous investigators indicated a high incidence or because of theoretical considerations in general.

OBSERVATIONS OF HEPATIC EDEMA

Seventy-nine cases (15 per cent) of the unselected group satisfied the criteria of intraparenchymal edema. The control series of cases, those of normal persons killed by violence, failed to reveal a single incidence of intralobular hepatic edema. The age incidence of the cases of hepatic edema was from 19 months to 75 years, with no especially prominent incidence in any particular age group. Postmortem fluid transudation appeared not to be a factor in the production of the edema inasmuch as edema was observed in cases in which autopsy was made within an hour to within seventeen hours after death. The majority

were about six hours post mortem. Edema did not occur with such frequency that it could be regarded merely as an agonal finding. The factor of absorption of large amounts of fluid either subcutaneously or intravenously administered can be disregarded inasmuch as most of the persons whose liver showed no edema had received as much or even more fluid in the several days before death as those whose liver was edematous.

Cardiac Failure.—The occurrence of intralobular hepatic edema in a considerable number (39 per cent) of cases of cardiac failure is contrary to the observations of Roessle and Gerlach.[8] They claimed that

TABLE 2.—*Results of Examination of Liver for Parenchymal Edema in Selected Cases*

Cause of Death	Total Number of Cases	Number in Which Hepatic Edema Was Found	Comment
Lipoid nephrosis	9	0	
Malignant nephrosclerosis	24	18	
Uremia other than that due to nephritis	36	14	Polycystic kidneys, 5; pyelonephritis, 7; carcinoma of bladder, 2
Diabetic coma	11	5	
Influenza	17	11	
Measles	12	2	
Scarlet fever	17	3	
Diphtheria	17	9	
Typhoid fever	12	2	
Acute lupus erythematosus	16	1	
Gastro-intestinal intoxication	29	1	
Exophthalmic goiter	21	9	
Addison's disease	5	0	
Laënnec's cirrhosis	16	3	
Status asthmaticus	6	5	
Anesthesia	8	4	Thoracotomy for pulmonary abscess under tri-bromethanol in amylene hydrate and nitrous oxide, 2; tonsillectomy under ether, 1; mastectomy under ether, 1
Thrombocytopenic purpura	9	5	
Burns	10	4	
Postoperative shock	3	0	

cardiac stasis causes only edema of Glisson's capsule and that intralobular edema occurs only in states of stasis associated with toxic processes. In our series no difference in the frequency of edema could be found between the cases of rheumatic failure in which the presence of a toxic factor might be postulated, and cases in which the myocardial lesions were of purely vascular origin. For this reason the hepatic edema can be fully accounted for on a mechanical basis.

Pulmonary Embolism.—It is noteworthy that hepatic edema is just about as frequent in cases of pulmonary embolism as in those of cardiac failure, which suggests that the sudden damming back of blood into

8. Gerlach, W.: Die Kreislaufstörungen der Leber: Oedem, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, no. 1, p. 121.

the inferior vena cava has the same effect as the prolonged stasis in chronic cardiac insufficiency.

Glomerulonephritis.—The frequent presence of hepatic edema in cases of glomerulonephritis in its various stages is not unexpected. It might reasonably be explained in the same way as the occurrence of edema is generally accounted for in glomerulonephritis inasmuch as all the persons with glomerulonephritis in whose liver edema was observed showed marked anasarca and ascites. It is of interest that, on the other hand, persons with chronic lipoid nephrosis with generalized edema did not present hepatic edema.

Malignant Nephrosclerosis; Uremia; Diabetic Coma.—The finding of hepatic edema in 75 per cent of the cases of malignant nephrosclerosis is striking. In view of the constant excessive elevation of the blood pressure the possibility of a cardiac origin has to be considered. However, except for three instances there was neither clinically nor anatomically any evidence of even terminal cardiac failure. Most of the patients died in dry uremia, two as a result of cerebral hemorrhage and three as a result of the uremia and cardiac failure. The question arose whether uremia in itself might be a factor responsible for hepatic edema. For this reason we studied uremia other than that due to glomerulonephritis or nephrosclerosis, such as that due to pyelonephritis and that due to polycystic kidneys. Although in this group there was present the additional factor of infection, the percentage of cases with hepatic edema (39) is far below that of cases of malignant nephrosclerosis with hepatic edema. One has to consider, therefore, that the increased permeability of the capillary wall in malignant nephrosclerosis is a feature characteristic of this disease and not merely a result of any associated condition such as uremia or cardiac failure. It is for this reason interesting to mention that Schürmann and MacMahon [9] in their recent article placed the greatest importance on an alteration of the vascular endothelium as the chief pathogenic factor in malignant nephrosclerosis. It is the damage of the endothelium as blood-tissue barrier (*Dysorie*) which is responsible for the characteristic vascular lesions as well as the parenchymal destruction. They also mentioned striking hepatic edema in one of their cases.

While we realize that uremia does not account for the strikingly high incidence of hepatic edema in the cases of malignant nephrosclerosis, the fact remains that 39 per cent of the cases of uremia did present hepatic edema. This is far above the average in the unselected cases and deserves further observation. The presence in uremia of an alteration in the chemical constitution of the blood suggested an inves-

9. Schürmann, P., and MacMahon, H. E.: Virchows Arch. f. path. Anat. **291**:471, 1933.

tigation of cases of diabetic coma with the associated chemical changes of the blood. Five of eleven cases presented hepatic edema, a percentage of 45, which is far above the average. Significantly, Moon [10] mentioned diabetic acidosis among toxemias of metabolic origin characterized by circulatory collapse associated with increased capillary permeability.

Infectious Diseases.—The study of infectious diseases gave unexpectedly low figures, contrary to the statement of Roessle, Eppinger and Gerlach. Only influenza showed a strikingly high percentage (64). This observation is interesting in view of the clinical picture of circulatory collapse presented by fulminating influenza. Underhill and Ringer [11] made studies of the blood in forty-three patients with influenza and were struck by the marked hemoconcentration, with the values of hemoglobin ranging to 140 and the red blood cell counts rising to 8,000,000. They believe that the circulatory collapse is caused by a decreased volume of blood effected by the transudation of plasma through the walls of the capillaries, chiefly of the lungs, the permeability of the walls having been increased in the course of the acute infection. Other pulmonary infections which are largely represented in our series revealed nothing significant. The same statement holds for other infectious diseases with severe toxemia, such as sepsis (bacteremia), subacute bacterial endocarditis, etc., as can be seen in tables 1 and 2. In the three cases in which hepatic edema accompanied scarlet fever it was associated with severe interstitial hepatitis and has to be regarded as collateral inflammatory edema. The high incidence of 53 per cent in cases of diphtheria is probably explained by the associated cardiac failure.

Peritonitis; Gastro-Intestinal Intoxication.—The negative findings in peritonitis indicate that the direct absorption of toxic products into the portal system does not necessarily cause hepatic edema. The single instance of hepatic edema in twenty cases of gastro-intestinal intoxication is rather disappointing in view of the severe hemoconcentration prevalent in these cases. One must not lose sight, however, of the fact that loss of plasma may occur elsewhere in the body.

Exophthalmic Goiter.—The high incidence of hepatic edema in cases of exophthalmic goiter (43 per cent) conforms with the observations of Roessle.[5] We also found occasionally the focal congestion of the liver described by Roessle and often strikingly subcapsular fibrosis. However, the latter was present in the same ratio in the cases which showed edema as in those which did not. Definite evidence that hepatic edema is responsible for the development of fibers could not be found, and it seems to us that the belief in a causal relationship rests so far

10. Moon, V. H.: Ann. Int. Med. **8**:1633, 1935.
11. Underhill, F. P., and Ringer, M.: J. A. M. A. **75**:1531, 1920.

merely on an interpretation of histologic facts. Roessle maintained that in exophthalmic goiter a toxin is elaborated by the disturbance in thyroid secretion which acts particularly on the liver because of the latter's detoxifying function.

Addison's Disease.—Because of the correlation between endocrine disturbance and hepatic edema, we examined eight cases of Addison's disease but did not find any instance of hepatic edema in these.

Laënnec's Cirrhosis.—The examination of Laënnec's cirrhosis was of special significance because Roessle's interest in hepatic edema took its origin in observations in this disease. In our, so far small, series of sixteen instances, intralobular hepatic edema was found only three times, a low incidence. Moreover, in two of these cases the edema was associated with myocardial insufficiency, and in the third death was due to influenza.

Status Asthmaticus.—A strikingly high incidence, five of six, is encountered in patients dying in so-called status asthmaticus with the characteristic clinical and anatomic findings. Failure of the right side of the heart does not fully account for the unusually high percentage, because in our series of cases with cardiac failure the incidence of hepatic edema was only 39 per cent. One might think of the effect of a histamine-like substance present in asthma, because intravenous injection of histamine produces hepatic edema, as shown by Eppinger and Leuchtenberger.[12]

Anesthesia.—In eight cases of death during operation regarded as due to the anesthesia hepatic edema was present four times. We hesitate to attribute too great significance to this high incidence, because of the small number of observations and because of the association with diseases of the respiratory tract in two of these cases, which in itself might have been responsible for the edema.

Thrombocytic Purpura.—The high incidence of hepatic edema (55 per cent) in nine cases of thrombocytopenic purpura is of interest because of the often expressed belief in the vascular etiology of this disease. Recently, Baehr, Klemperer and Schiffrin[13] reported diffuse platelet thrombosis of the capillaries and arterioles in four cases, in three of which there was striking hepatic edema.

Burns.—The relatively high incidence of hepatic edema in cases of death following burns seems to conform with the observations of Eppinger. However, death occurred soon after the accident only in two cases.

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12. Eppinger, H., and Leuchtenberger, R.: Ztschr. f. d. ges. exper. Med. **85**:581, 1932.

13. Baehr, G.; Klemperer, P., and Schiffrin, A.: Tr. A. Am. Physicians, 1936, to be published.

Shock.—The question of the relationship of shock and hepatic edema, so prominently stressed by Eppinger, deserved our special attention. It was difficult, because of the nature of our material, to collect a sufficiently large number of such instances. Only in three cases in which death occurred subsequent to operation were the clinical criteria of shock satisfied: They presented at necropsy pulmonary congestion and edema (the anatomic characteristics of shock as stressed by Moon and Kennedy [14]) in the absence of hemorrhage or any anatomic lesion to account for the collapse. It is noteworthy that in these cases we did not find hepatic edema. In three of seven cases of acute coronary occlusion terminating fatally with the picture of shock, hepatic edema was present. This incidence does not exceed that found in cases of cardiac failure in general.

Unexplained Hepatic Edema.—Short mention must be made of the fact that the most conspicuous hepatic edema was observed in two cases of unexplained death which were investigated by the medical examiner of New York City.

COMMENT

In a consideration of the significance of hepatic edema attention must be called to its frequency in cardiac failure. In this condition the mechanism of its development is evidently governed by physical factors. Undoubtedly in these instances the concept does not hold that intralobular hepatic edema represents serous hepatitis. However, microscopically there are neither qualitative nor quantitative differences between these cases of mechanical edema and those which have to be accounted for by a different mechanism. The high incidence of hepatic edema in cases of uremia and diabetic coma points to the rôle played by metabolic toxic products or by chemical changes of the blood in altering the permeability of the vascular wall. A similar influence is exerted by certain disturbances of internal secretion, evidenced by the positive findings in exophthalmic goiter. On the other hand, in most bacterial infections, even those with striking toxicity, hepatic edema was not conspicuous in our series, contrary to the general statements of Roessle. Therefore the etiology does not "speak for the inflammatory nature of the nonmechanical hepatic edema," as Roessle [4] maintained. Furthermore, we were not impressed by an association of enlarged Kupffer cells and hepatic edema, a feature stressed by Roessle. In view of these considerations, we cannot accept his concept of the inflammatory nature of hepatic edema.

The term "primary edema" might be chosen to indicate that the plasma transudation is due to primary increased permeability of the

14. Moon, V. H., and Kennedy, P. J.: Arch. Path. **14**:360, 1932.

capillary wall, while "mechanical edema" would indicate that the transudation is due chiefly to alterations of the hydrostatic pressure within the capillary lumen.

The association of primary edema with visible damage to the capillary wall is not easily ascertained. Swelling, as well as necrobiosis of Kupffer cells, has been seen by us in cases with and without hepatic edema. Destruction of the fine reticulum fibers, on the other hand, was not definitely apparent even in cases of striking edema. Occasionally only a few delicate fibers were seen floating within the dilated Disse spaces, as if they were torn from their connection with the other fibers. Also, we must entertain great reserve in regard to liver cell changes associated with edema. Liver cell degeneration or necrosis is certainly not frequent in cases of acute primary edema. Occasionally, individual liver cells are found to be shrunken and without nuclei. But similar lesions are found without edema. In fact, focal necrosis was often encountered in sections of liver which did not show even the slightest edema. In mechanical edema, on the other hand, we found atrophic liver cells frequently and necrosis occasionally, changes similar to those seen in the various phases of chronic passive hyperemia.

The concept of the formation of collagenous fibers within the serous exudate seems to us to be only a matter of interpretation. We did not see in human pathologic material histologic pictures which could be regarded as showing the early phase of the fiber formation.

The question whether primary hepatic edema more frequently represents only a local increase than a systematic increase in capillary permeability is important. At present we are unable to answer it. We have tried to ascertain its association with pulmonary edema and have found that only seven of the seventy-nine cases in which hepatic edema was found revealed no pulmonary edema at postmortem examination. However, no significance can be attributed to this observation in view of the exceedingly high incidence of pulmonary edema as a terminal event.

Our studies are in accord with those of Roessle in the observation that intralobular edema occurs rather frequently in the liver. We cannot agree, however, as to the type of morbid process in which it is most prominent. Neither can we accept the significance which he ascribes to edema in the pathogenesis of acute and chronic hepatic lesions. Nevertheless, we must recognize that mainly because of his investigations hepatic edema will receive from pathologists the attention which it deserves as the only histologic evidence of increased capillary permeability. The significance of the latter is already recognized in experimental and clinical medicine. The morphologic recognition of this altered state in various diseases such as malignant nephrosclerosis, diabetic coma, uremia and others in which it is present, as revealed in

our studies, might be of interest for clinical investigation. It is evident that similar morphologic studies should be made in other organs regarding the state of permeability of the capillary wall.

SUMMARY AND CONCLUSIONS

Sections of liver obtained in 505 consecutive autopsies were studied for the presence of intralobular hepatic edema. This was found in seventy-nine cases, or 15 per cent.

Two types of intralobular hepatic edema occur: (1) that due to the same physical factors which govern the development of edema in circulatory failure and (2) that due to a primary increased permeability of the vascular wall caused by various factors not yet fully recognized. It is suggested that the first type be referred to as mechanical edema and the second as primary edema. Its designation by Roessle as serous hepatitis is not appropriate.

Mechanical hepatic edema occurred in almost half of the aforementioned seventy-nine cases; no difference in frequency of this condition was noted in the cases of circulatory failure due to rheumatic and those due to vascular myocardial lesions.

Primary hepatic edema has been observed to occur in a variety of morbid conditions, among which the most important are malignant nephrosclerosis, influenza, diabetic coma, uremia and exophthalmic goiter. In the infectious diseases, except for influenza, it is not conspicuous.

Primary hepatic edema is of significance as the only morphologic evidence of increased permeability of the capillary wall.

CHEMICAL AND PATHOLOGIC STUDY OF PNEUMONOCONIOSIS

WITH SPECIAL EMPHASIS ON SILICOSIS AND SILICOTUBERCULOSIS

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Since Hippocrates' time it has been known that "asthmatic" or "phthisic" pulmonary disease results from breathing dust in mines and other sources where the rock crust of the earth is brought into fine powder. For a historical bibliography reference may be made to Collis,[1] Higgins, Lanza, Laney and Rice,[2] Hoffman,[3] Willis,[4] Harrington and Davenport[5] and especially the exhaustive compilations of Davis, Salmonsen and Earlywine.[6]

In recent times it has been observed that there are many types of dust that cause irritation, in addition to pulverized rock and quartz. Even numerous organic substances have been found to cause disease. Lochtkemper and Teleky[7] stated that any dust is harmful if the exposure is sufficiently long and intense. The organic dusts, however, usually cause transient irritation and result in no further trouble after they are expelled or the person is removed from the environment.

From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium and the Jasper County (Mo.) Tuberculosis Hospital.

1. Collis, E. L.: Pub. Health, London **28**:252 and 292, 1914-1915.

2. Higgins, E.; Lanza, A. J.; Laney, F. B., and Rice, G. S.: Silicosis Dust in Relation to Pulmonary Disease Among Miners, Bulletin 132, U. S. Dept. Interior, Bureau of Mines, 1917, pp. 22 and 116.

3. Hoffman, F. L.: The Problem of Dust Phthisis in the Granite-Stone Industry, Bulletin 293, U. S. Dept. Labor, Bureau of Labor Statistics, 1922.

4. Willis, H. S.: Medicine **9**:413, 1930.

5. Harrington, D., and Davenport, S. J.: Review of Literature on Effects of Breathing Dust with Special Reference to Silicosis, U. S. Dept. Interior, Bureau of Mines, 1935, Information Circulars 6835, 6840 and 6848.

6. Davis, G. G.; Salmonsen, E. M., and Earlywine, J. L.: The Pneumonokonioses (Silicosis): Bibliography and Laws, Chicago, Industrial Medicine, Inc., 1934; The Pneumonokonioses (Silicosis): Literature and Laws of 1934, Chicago, Chicago Medical Press, 1935.

7. Lochtkemper, I., and Teleky, L.: Arch. f. Gewerbepath. u. Gewerbehyg. **3**:600, 1932.

Of the inorganic dusts, finely powdered quartz (silicon dioxide), asbestos (hydrated magnesium silicate), sometimes with iron, calcium and aluminum, and sericite or secondary mica (partly hydrated alkali aluminum silicate) seem to be most detrimental so far as industrial work is concerned. Usually these substances are associated with others.

To these three dusts may be added other questionable substances, about the action of which little is known. In this category are the feldspars (alkali aluminum silicates), which on hydration yield clays (hydrated aluminum silicates). The usual formula for this change is $KR + H_2O + CO_2 = HR + K_2CO_3 + SiO_2$, in which R indicates aluminum silicate. Partial hydration of feldspar yields sericite, which Jones [8] accused of being the active agent in the causation of silicosis.

There is strong suspicion that a group of minerals like the feldspars, making up nearly half the crust of the earth by weight and yielding on weathering, in addition to the clays, silicon dioxide and sericite, may be pathogenic. Then there are many minerals, such as white and black mica, slate, shale, tripoli, talc, meerschaum, corundum, carborundum and sillimanite, as well as many semiprecious stones, that may be suspected of having injurious effects on the body.

Another group of substances, more or less inert, includes carbon or coal, iron with hematite (iron oxide) and perhaps certain silicates. Although much is still to be learned of their action, they are in general inert or sluggishly active in causing fibrosis.

There is still another group thought to be harmless, particularly with regard to increasing the hazards of tuberculosis. While coal and iron pigment may be more or less neutral in this regard, limestone, marble, calcium carbonate, gypsum and calcium sulfate, if not actually prophylactic against tuberculosis, are per se not detrimental. If any trouble arises from these minerals, it is most likely due to contamination with silica. The work of Gardner and Dworski,[9] as well as that of others, on marble-dust, seemed to indicate that most of this dust is soon dissolved but that there is a small fraction of silica that after a long time may lead to the formation of nodules.

Finally, there is a group of substances which are acutely toxic, such as phosphorus, zinc, lead, manganese, mercury, arsenic and radioactive ores. Their effects, however, are well known in toxicology and need no further attention here.

While it is difficult and hazardous in the present state of knowledge to adopt any fixed classification or to attempt new ones, it may be convenient to use a grouping based on the chemical origin of the irritant.

8. Jones, W. R.: J. Hyg. **33**:307, 1933.

9. Gardner, L. U., and Dworski, Morris: Am. Rev. Tuberc. **6**:782, 1922.

This is in accord with the classification by Badham.[10] Tentatively, the following grouping is suggested:

Pneumonoconiosis, meaning "dusty lungs," including all diseases due to dusts.

Silicosis, caused by silicon dioxide.

Silicatosis, caused by silicates in general.

Anthracosis, caused by carbon.

Siderosis, caused by iron.

Asbestosis, caused by asbestos.

Tuberculosis or anthracosis, for instance, superimposed on silicosis may be indicated as silicotuberculosis or silico-anthracotuberculosis, depending on the combination of irritants involved. As a matter of fact, the majority of processes are mixed and nearly always involve the tubercle bacillus.

This report is limited to the disease produced by silicon dioxide (with or without sericite), independently or with the dampening effect of dusts, such as coal, iron, etc., on the one hand, and the aggravating effect of tuberculosis, on the other.

The rôle of sericite is controversial, but it does not concern the problems of this paper, so it will not be discussed here.

As quartz-rock is usually thought to be insoluble in water and the damage seems to be due to the soluble silica, an explanation of the solubility is highly desirable.

By a reduction in the size of the particles the surface may be so increased that an adequate quantity passes into solution to produce a toxic effect. King and his associates[11] have demonstrated this in animals by finding silica in the urine after parenteral injection. Boehme and Kraut[12] reported from a twofold to a threefold increase in the silica content of the blood of patients with silicosis.

In support of this theory are numerous instances in nature of silica in solution. Certain waters contain large quantities of it, especially volcanic springs and geysers, many having as much as 1 part in 2,000, and all water contains some. The action of certain enzymes (like those of soil bacteria) causes it to go into solution rather readily. In weak alkaline solutions, according to Haynes,[13] the solubility of silicon dioxide to form silicic acid is increased. In former geologic ages silica virtually permeated the crust of the earth. Flint, jasper, agate, onyx, chert, jasperoid and many other minerals and the "petrified" forests

10. Badham, C.: Notes on a Fine Type of Fibrous Pneumonokoniosis Produced by Silicates and Other Minerals, Publication 13, Studies in Industrial Hygiene, Report of Director-General of Public Health, New South Wales, 1927.

11. King, E. J.; Stantial, H., and Dolan, M.: Biochem. J. **27**:1007, 1933.

12. Boehme, A., and Kraut, H.: Arbeitsphysiol. **5**:269, 1931.

13. Haynes, F.: J. Hyg. **31**:96, 1931.

and "silicated" shells of animals are largely the result of penetration by hydrated silicic acid, which ultimately loses its water and becomes crystallized silicon dioxide.

These phenomena may afford a basis of explanation of the action of silica in living tissues. It surely offers a better explanation than the older theory of the sharpness of the particles, conceded to be untenable by modern workers. Gardner,[14] for example, looked on soluble silica as a direct poison to the cell. Gye and Kettle[15] stated that their work was based on the fact that colloidal silica is a poison to the cell. Heffernan[16] expressed the opinion that a physiochemical change is brought about by the colloidal silica, which becomes hydrated at the expense of the cell protoplasm. It is possible that the colloid may produce a dehydrating effect on the cell or may actually penetrate the finer structures of the cell, as it does in petrification. All living matter seems to be subject to "petrifaction" by silicic acid, and one of the greatest enigmas in the problem of silicosis is that nature has failed to protect living forms against one of their most common environmental factors. In fact, many forms of life seem to use silica in their metabolism. Diatoms, horsetails and sponges are heavily silicated, as well as feathers, hoofs, nails, etc., of the higher forms of life.

In addition to the problem of solubility, there are other factors that enhance the development of silicosis. Even though animals seem to be subject to it they vary a great deal in this respect.

As a result of anomalies of the upper respiratory tract that necessitate mouth breathing, more dust enters the lung. Some persons may also have better pulmonary activity—muscular and ciliary— than others. The pulmonary activity is more sluggish in older than in younger persons. As pointed out by Steuart[17] and others, the older the man the sooner the disease becomes manifest.

More important, however, is the presence of disease of the bronchial tract. In cases of ulceration or a disease focus there is less function of the bronchial ramus involved, and, hence, less opportunity to expel inhaled dust. As tuberculosis is one of the most common causes of damage to the bronchi and the pulmonary epithelium, tuberculous infection is particularly dangerous in an environment of finely divided silica. Other long-standing infections, such as bronchitis, disease of the sinuses, etc., also tend to impair normal function.

It may be well to refer to the work of Macklin[18] on the "dynamic bronchial tree," in which he showed that when the lung is healthy

14. Gardner, L. U.: J. A. M. A. **101**:594, 1933.
15. Gye, W. E., and Kettle, E. H.: Lancet **2**:855, 1922.
16. Heffernan, P.: Tubercle **11**:61, 1929.
17. Steuart, W.: Arch. Radiol. & Electroth. **27**:277, 1923.
18. Macklin, C. C.: Am. Rev. Tuberc. **25**:393, 1923.

the bronchi are cleaned by normal physiologic methods but that when hyperplasia of the lymph nodes, fibrosis or other changes occur which interfere with normal resilience, the ability to clean the bronchi is diminished.

In addition to the effects of disease, individual, racial and familial differences must undoubtedly be considered. Jarvis,[19] for instance, mentioned a racial difference in the granite workers of Barre, Vt.

The actual mechanism of the disease has been well described in numerous publications by Gardner, Kettle, Simson, Mavrogordato, Policard and others, a review of which was made by Belt [20] as well as by Harrington and Davenport.[5] The dust that remains in the lungs passes beyond the cilia into the finer bronchioles or the alveoli, from which it is removed by phagocytosis and expelled in the sputum or carried toward the hilus along the lymphatics.

There is a difference of opinion regarding the phagocytic activity produced by fine silica. Gardner [21] expressed the belief that quartz produces active phagocytosis and brisk activity of the phagocytes, while Mavrogordato [22] and Policard [23] contended that the effect of poisoning is so rapid that the activity of the phagocyte is soon ended and the "mummified" cell or plaque of cells becomes entirely inactive and may be expelled through the bronchus or pass upward along the lymphatics. It seems that the quantitative aspect must be considered to reconcile these views.

There are an accumulation of cells containing dust in the hilar lymph nodes and a backing up in the lymphatics toward the periphery, like "log jams in a river," as Mavrogordato [22] expressed it. In these "jams" fibroblasts are formed and develop into fibrous tissue in the form of whorls. As the blockage of the lymphatics continues, there comes a time when phagocytes are retained in the parenchyma and the formation of whorls extends into the tissue of the lung.

It was contended by Simson and his associates [24] that the first fibrosis associated with silicosis takes place in the hilar lymph nodes, where the greatest number of lymphatics meet. This produces a greater collection of cells, a greater concentration of the silica and, therefore,

19. Jarvis, D. C.: Am. J. Roentgenol. **8**:244, 1921.

20. Belt, T. H.: Am. J. M. Sc. **188**:418, 1934.

21. Gardner, L. U.: J. Indust. Hyg. **14**:18, 1932.

22. Mavrogordato, A.: Studies in Experimental Silicosis and Other Pneumokonioses, Publication 15, South African Institute for Medical Research, 1922.

23. Policard, A.: Presse méd. **41**:88, 1933.

24. Simson, F. W.; Strachan, A. Sutherland, and Irvine, L. G.: Silicosis in South Africa: A Symposium on the Histo-Pathology, Pathological Anatomy and Radiology of the Disease, Johannesburg, South African Institute for Medical Research, 1931.

the first definite fibrosis. Later the lymphatics along the arteries and bronchi become involved. The bends of the lymph vessels and the lymph follicles become clogged with "mummified" cells, resulting in accumulations of silica-bearing cells at these points. Simson also mentioned "islets of phagocytes" in this lymphoid tissue. The process goes on until most of the lymphatic channels are stopped, and then nodules begin to appear in the parenchyma or beneath the pleura as the lymph current turns in the direction of the latter. Finally, there is a piling up of silica in the tissues because all the avenues of escape are blocked.

This general course may be modified by the type of dust; for example, asbestos produces bronchiolitis first; coal and iron, rather inert themselves, block the lymphatics and dampen the action of silicosis, and tuberculosis aggravates involvement of any type and leads to necrosis and ulceration.

Recently, medical and legal attention has been directed toward the field of chemistry and physicochemistry for the solution of the problem of pneumonoconiosis. The total silica content of the various parts of the respiratory tract is significant in cases of borderline conditions.

We have made chemical analyses in a group of patients who worked in a wide range of inorganic dusts, as well as in a series of persons used as controls, having other chronic pulmonary diseases, who would be considered normal from the standpoint of silicosis. The results of the clinical, roentgenologic, gross and microscopic and chemical examinations have been correlated.

METHOD

The lungs were removed from the body, and a roentgenogram was taken post mortem after moderate inflation. The lungs were then hardened in a dilute solution of formaldehyde U. S. P. (4 per cent) for two days and sectioned laterally for gross study. Sections were cut about 2 cm. in thickness, or less if more careful study was demanded. The surface, color, adhesions and consolidations were described. Then the size, shape, character and appearance of any internal pathologic structures were also recorded.

Tissue was taken for analysis that represented as wide a variation of involvement as possible. For instance, pneumonic, fibroid, pigmented and "normal" areas and the regions of lymph nodes were selected for chemical analysis, and representative sections were taken for microscopic study. If calcification was present the tissue was decalcified; otherwise it was embedded in paraffin, and stained with the appropriate methods.

ANALYTIC PROCEDURE

The specimens are prepared by drying in a vacuum oven after they have been passed through a meat-chopper. The dried tissue is then reduced to a fine powder in a small mill. An iron mortar and pestle is used for the lymph nodes. To insure uniformity the lung is ground until all of it passes through a 40 mesh sieve. After thorough mixing, the powder is dried to constant weight at from 105 to

110 C. and is bottled. Removal of excessive amounts of connective tissue facilitates grinding. Lungs preserved in a solution containing a considerable quantity of glycerine are washed thoroughly with distilled water before drying. Lungs rich in fatty material may be defatted with a solvent, such as acetone, before or after the preliminary drying, if the appropriate correction is made for the amount of fat removed.

The method for the gravimetric determination of total silica is a wet ashing procedure with a mixture of nitric and perchloric acids. The residual perchloric acid acts as an effective dehydrating agent for the silica and a solvent for the metals and their salts. The silica in the residue is then estimated on the basis of the loss of weight during treatment with hydrofluoric acid.

From 5 to 15 Gm. of dried lung is weighed rapidly in a 250 cc. pyrex beaker. Twenty-five cubic centimeters of chemically pure concentrated nitric acid is added with stirring. Foaming follows immediately and is controlled by the occasional addition of 1 or 2 drops of capryl or octyl alcohol. The reaction becomes vigorous but soon subsides. The beaker is then placed on a hot-plate, and the nitric acid is allowed to boil briskly. A watch-glass supported over the beaker by means of small bent glass rods prevents loss from spattering without interfering with evaporation. If large quantities of lung tissue are treated, additional nitric acid is added at this point. In any case, the nitric acid is boiled until 10 or 20 cc. remains in the beaker. Thirty cubic centimeters or more of a 60 per cent solution of chemically pure perchloric acid is added to the hot reaction mixture, and boiling is continued until the nitric acid has all been evaporated. The vigorous reaction which occurs at this point is controlled by decreasing the amount of heat. Capryl or octyl alcohol must not be used. Gentle boiling is continued for thirty minutes after the solution becomes colorless or light yellow-green. Sufficient perchloric acid must be used to prevent drying at this stage.

After the beaker and its contents are cooled, from 150 to 200 cc. of distilled water is added. The mixture is allowed to boil for five or ten minutes. The silica is removed from the hot solution by filtration and is washed five times with small quantities of boiling 5 per cent hydrochloric acid. It is then ignited to constant weight in a platinum crucible.

The purity of the silica is determined by adding hydrofluoric acid and a drop of sulfuric acid, evaporating to dryness and again igniting to constant weight. A single treatment with 5 cc. of the acid is usually sufficient to remove all the silica.

Most of the analyses have been made in duplicate, and some in triplicate. The results have corresponded closely, in spite of the fact that different quantities were used to begin each check analysis.

When sufficient quantities of tissue were not available for gravimetric analysis the colorimetric method of King [25] was employed.

The ashing of the dry specimen has also been carried out in the majority of the cases, and the silicon dioxide content determined on the basis of the amount of ash. This procedure is included for purposes of comparison because some authors have calculated the values on this basis. Without our taking space to give these values, they may be approximated by multiplying the percentage of silica in dry tissue by a factor ranging from 10 in cases of severe silicosis to 50 in those of the normal lung.

For example, dry normal tissue contains about 5 per cent ash and 0.1 per cent silica. The silica constitutes, therefore, 2 per cent of the ash. In cases of silicosis

25. King, E. J.: J. Biol. Chem. **80**:25, 1928.

these values may rise as high as 20, 5 and 20 per cent, with average values of about 10, 1 and 10 per cent, respectively. The results of such determinations are shown in table 1.

The percentage of silica in the moist lung may be calculated by remembering that the weight of the dry tissue is from 15 to 20 per cent of that of the moist.

Petrographic analysis and micro-incineration, although offering great promise for experimental work, have until the present given disappointing results. As Irwin [26] has pointed out, the detrimental silica is hydrated and cannot be seen by these methods. It must be understood, therefore, that this hydrated silica cannot be seen at all and that no particles less than 5 microns can be studied by the petrographic microscope. These methods, therefore, add only presumptive evidence.

TABLE 1.—*Results of Determination of the Silica Content of the Lungs of Persons Representing Three Types of Occupation*

	Ash Content of Dry Tissue, Percentage	Silica Content of Dry Tissue, Percentage	Ratio of Silica to Ash, Percentage
Normal person	5.0	0.1	2.0
Stonecutter, mixed quartz	13.3	1.0	7.5
Lead and zinc miner, pure silica	8.2	1.2	14.6

RESULTS OF ANALYSIS

In table 2 are recorded the observations on the "normal" lungs of four infants and one woman and on the lungs and lymph nodes of fifteen tuberculous patients. As pointed out by King,[25] McNally and Bergman,[27] Fowweather [28] and others, there seems to be a normal level of silica in the tissues. This has been found to be about 1 mg. per gram of dried lung (0.1 per cent). In the kidney of a patient with silicosis (case 22, table 3) there was only 0.4 mg. per gram of dried tissue (0.04 per cent)—a fair average for most of the tissues free from lymphoid or connective tissue. The spleen of an infant contained 0.8 mg. per gram (0.08 per cent). McNally and Bergman [27] found an average of 0.034 per cent in the lungs of fourteen infants. According to Guersching and Kraut,[29] the silica level is regulated by the parathyroid glands and may vary slightly from one person to another.

The results for the lungs and lymph nodes of fifteen tuberculous persons from 9 to 72 years of age were not in every sense "normal." The percentages for the first patient, a child with healing lesions of childhood tuberculosis, were normal for both the lungs and the lymph nodes. In cases 7, 8 and 10, in which adults aged 22, 23 and 32, respectively, were represented, an increase in the content of the hilar lymph nodes to 2.3, 2.9 and 2.6 mg. per gram of dried tissue, respec-

26. Irwin, D. A.: Canad. M. A. J. **31**:140, 1934.

27. McNally, W. D., and Bergman, W. L.: J. Indust. Hyg. **17**:171, 1935.

28. Fowweather, F. S.: Refractories J. **10**:173, 1934.

29. Guersching, J., and Kraut, H.: Arch. f. exper. Path. u. Pharmakol. **167**: 146, 1932.

TABLE 2.—*Clinical and Pathologic Data and the Results of Analysis for Silica Content of Dried Tissue from Twenty Persons Used as Controls*

Case	Age, Years	Occupation	Gross Pathologic Condition	Tissue Analyzed	Residue of Ash in Dry Tissue, %	× Silicon Dioxide Fraction in Residue	= Silicon Dioxide in Dry Tissue, %		Hydrofluoric Acid Residue in Dry Tissue, %
							Lung	Other Organs	
1	1—	.....	Normal lung	Lung	....	....	0.07		
2	1—	.....	Normal lung	Lung	....	....	0.09		
3	1—	.....	Normal lung	Lung	0.14	0.84	0.12	....	0.02
4	1—	.....	Normal lung	Lung	....	....	0.16		
5	56	Nurse	Normal lung	Pooled lung	0.57	0.19	0.11	....	0.46
				Pooled lung	0.59	0.19	0.11	....	0.48
6	9	School child	Healed childhood tuberculosis....	Pooled lung	0.10	0.88	0.09	....	0.01
				Pooled lung	0.10	0.80	0.08	....	0.02
				Hilar lymph nodes	....	....	....	0.10	
				Spleen	....	....	....	0.08	
7	22	Factory, etc.	Fibrocaseous and ulcerative tuberculosis	Hilar lymph nodes	....	....	....	0.23	
8	23	Truck driver	Fibrocaseous and ulcerative tuberculosis	Hilar lymph nodes	....	....	....	0.29	
9	26	Housewife	Fibrocaseous tuberculosis	Pooled lung	0.13	0.31	0.03	....	0.10
				Pooled lung	0.13	0.25	0.03	....	0.10
10	32	Plasterer	Fibrocaseous tuberculosis	Hilar lymph nodes	....	....	....	0.26	....
11	36	Housewife	Fibrocaseous tuberculosis	Pooled lung	0.05	0.54	0.03	....	0.02
				Pooled lung	0.04	0.64	0.03	....	0.01
12	41	Housewife (Negro)	Caseous bronchopneumonia	Pooled lung	0.05	0.47	0.02	....	0.03
				Pooled lung	0.05	0.47	0.02	....	0.03
13	46	Housewife	Fibrocaseous and ulcerative tuberculosis	Pooled lung	0.07	0.77	0.05	....	0.02
				Pooled lung	0.07	0.78	0.05	....	0.02
14	45	Housewife	Fibrocaseous and ulcerative tuberculosis	Pooled lung	0.09	0.90	0.08		
				Pooled lung	0.09	0.86	0.08		
				Hilar lymph nodes	....	....	....	0.60	
15	47	Shipping clerk	Fibrocaseous and ulcerative tuberculosis	Pooled lung	0.07	0.83	0.06	....	0.01
				Pooled lung	0.08	0.79	0.06	....	0.02
				Hilar lymph nodes	....	....	....	0.67	
16	54	Machinist	Fibrocaseous tuberculosis	Pooled lung	0.13	0.81	0.10	....	0.03
				Pooled lung	0.12	0.76	0.09	....	0.03
				Hilar lymph nodes	....	....	....	0.72	
17	63	Post-office clerk	Fibrocaseous tuebrculosis	Pooled lung	0.19	0.60	0.11	....	0.08
				Pooled lung	0.18	0.75	0.13	....	0.05
18	65	Housewife	Fibrocaseous and fibrous tuberculosis	Upper part of lung	0.12	0.90	0.11	....	0.01
				Upper part of lung	0.16	0.61	0.11	....	0.05
				Lower part of lung	0.22	0.64	0.12	....	0.10
				Lower part of lung	0.22	0.64	0.12	....	0.10
				Hilar lymph nodes	....	....	....	0.50	
19	67	Pharmacist	Calcified and fibrous tuberculosis	Pooled lung	0.22	0.67	0.14	....	0.08
				Pooled lung	0.20	0.70	0.14	....	0.06
20	72	Farmer	Multiple calcifications	Pooled lung	0.76	0.82	0.62	....	0.14
				Pooled lung	0.80	0.80	0.64	....	0.16
				Hilar lymph nodes	....	....	....	0.54	

The number of milligrams per gram of dry tissue may be obtained by multipiying the percentage of silicon dioxide in the third column (double) of values by 10.

tively, was shown. As the age advanced the silica content of the lymph nodes increased to about 6 mg. per gram of dried tissue in middle life, suggesting that there is a gradual accumulation of silicon dioxide (probably including silicates). These observations are in general agreement with those of Woskressensky [30] and King and his associates.[31] In the lungs of most of the patients in this group the silica content was low. Except in case 20, the amount in the lungs ranged from 0.2 to 1.4 mg. per gram. Study of the structure of the various specimens and the silica content of different regions of the lung showed that some of the wide variation seemed to be due to the dilution of the silica by the action of inflammatory tissue. This was true also in the cases of silicosis with acute pneumonia, in which the silica was diluted from five to seven times (as shown in table 3, cases 4 and 34). The more acute the reaction, the lower was the silica content. The caseous material and the cellular infiltrates appeared to be the diluents, because in fibroid lungs the values were more normal, being only slightly lower than those for other types of lung tissue. The silica content of the blood, lymph, etc., is therefore lower than that of the fixed tissues of the lungs. The value given for the silica content of normal blood by Boehme and Kraut [12] is 1.8 per cent of the ash (0.04 per cent of dry blood). McNally and Bergman [27] however, found an average silica content of only 0.013 per cent of dried blood.

The normal nonvolatile residue of hydrofluoric acid ranged from 0.01 to 0.03 per cent, but in the two men (post-office clerk and pharmacist), aged 63 and 67, respectively, this residue rose to half the value for silica. In the last control patient (case 20) the content of the parenchyma of the lung was unusually high. There was widely scattered, calcified nodular tuberculosis, which may have impaired the clearing of the bronchial tract during the greater part of the man's life. This may have caused retention of finely powdered soil (including silicates), inhaled during his long life as a farmer. On the other hand, Wells, Long and DeWitt [32] have cited figures showing an increase in the silica content of tuberculous tissue. There was definite and marked fibrosis characteristic of silicosis in the bronchopulmonary and hilar lymph nodes. Pancoast and Pendergrass [33] mentioned such conditions in farmers and those living in the region of sand-storms.

In table 3 we have recorded the results for eight groups of patients. Group *A* includes eight patients with a history of exposure

30. Woskressensky: Centralbl. f. allg. Path. u. path. Anat. **9**:296, 1898.

31. King, E. J.; Stantial, H., and Dolan, M.: Biochem. J. **27**:1002, 1933.

32. Wells, H. G.; Long, E. R., and DeWitt, L. M.: The Chemistry of Tuberculosis, Baltimore, Williams & Wilkins Company, 1932.

33. Pancoast, H. K., and Pendergrass, E. P.: Pneumoconiosis (Silicosis): A Roentgenological Study with Notes on Pathology, New York, Paul B. Hoeber, Inc., 1926.

to dust none of whom showed what was considered to be silicosis. Most of these patients did dusty work, as shown by the residue of hydrofluoric acid, in each case, but the silica content was not much above the normal, except in cases 7 and 8.

The same statement may be applied to the eight patients of group *B*, except that in these instances there was evidence of silicosis. There may have been involvement only of the lymph nodes, but the changes were definite.

The other groups include the following: group *C*, a patient with apparently uncomplicated silicosis, described later in detail; group *D*, a patient with apparently uncomplicated anthracosilicosis; group *E*, five patients working in rock or granite, having silicotuberculosis; group *F*, twelve patients working in pure silica, having silicotuberculosis; group *G*, three patients working in iron ore, and group *H*, two patients having mixed occupations involving work in "pure silica" and coal dust.

The first column of values in table 3 represents the residue after digestion, expressed in percentages of the original dry tissue. The values in this series ranged from 0.1 to 3.5 per cent, and the material was made up of two types, viz., that volatilized by treatment with hydrofluoric acid and the nonvolatile residue. The first type was pure silicon dioxide and many silicates that had been changed to silicon dioxide. The silicon dioxide fractions of the first residues are shown in the second column of values; that is, for the second specimen 0.35 of the 0.14 per cent shown in the first set of figures in the table represents the amount of silicon dioxide in the dry tissue, or 0.05 per cent, as recorded in the third column of values. This quantity may be expressed in milligrams per gram of dry tissue by multiplying it by 10. The third column of values is double, showing the results of analyses of the lung on the left and those of other tissues on the right, expressed in percentages. The fourth column then records the difference between the total residue in the first column of values and the volatile silicon dioxide in the third and represents the residue not volatilized by hydrofluoric acid. It consisted, perhaps, of a few insoluble silicates—those of iron, manganese, carborundum, emery (corundum), etc. The last column shows values expressed in fractions, the numerator of which represents the ratio of the silica content to the normal and the denominator, the ratio of the nonvolatile residue of hydrofluoric acid to the normal. The number on the right is the combined ratio, expressed in percentage. The groups will be considered in order.

GROUP *A.—Patients with pneumonoconiosis without silicosis.*

Although there are relatively few of the patients on whom we do not have complete data, only pertinent material is used for the sake of conciseness and brevity.

TABLE 3.—*Clinical and Pathologic Data and the Results of Analysis for Silica Content of Dried Tissues from Forty Persons with Diseases of the Lungs Caused by Dust*

Case	Age, Yrs.	Occupation	Wassermann Reaction	Period of Exposure, Yrs.	Period After Exposure, Yrs.	Color of Lung	Gross Pathologic Condition	Microscopic Pathologic Condition	Tissue Analyzed	Residue in Dry Tissue, %	× Silicon Dioxide Fraction in Residue	= Silicon Dioxide in Dry Tissue, % Lung	Other Organs	Non-volatile Hydrofluoric Acid Residue, %	Silica Residue Coefficient	Silica Residue Percentage
Group A. Pneumonoconiosis Without Silicotic Fibrosis																
1	29	Machinist and asbestos worker	—	5.5	3	Gray	Pulmonary tuberculosis	Tuberculosis	Pooled lung	0.02	0.60	0.012	....	0.008	0.1/0.2	50
									Pooled lung	0.02	0.86	0.019	....	0.001		
									Hilar lymph nodes	....	....	....	0.23			
2	34	Copper miner	—	Many	7	Gray	Pulmonary tuberculosis	Tuberculosis	Pooled lung	0.14	0.35	0.05	....	0.09	0.4/4	10
									Pooled lung	0.13	0.31	0.04	....	0.00		
									Hilar lymph nodes	....	....	....	0.32			
3	27	Machinist	—	7	Many	Gray-yellow	Silicotuberculosis	Tuberculosis	Pooled lung	0.18	0.74	0.13	....	0.05	1/2.5	40
									Pooled lung	0.17	0.74	0.12	....	0.05		
4	60	Boilermaker in lead and zinc mines	—	?	Many	Black	Anthracosis and carcinoma	Carcinoma	Left lung	0.49	0.28	0.14	....	0.35		
									Left lung	0.54	0.29	0.15	....	0.39		
									Right lung	0.08	0.83	0.07	....	0.01	1/18	5
									Right lung	0.10	0.82	0.08	....	0.02		
									Hilar lymph nodes	....	....	....	0.73			
5	64	Janitor	—	45	3	Brown-black	Bronchiectasis	Anthracosis	Pooled lung	0.25	0.68	0.17	....	0.08	1/4	25
6	59	Molder	—	Many	3	Brown-black	Emphysema	Emphysema	Pooled lung	0.30	0.61	0.18	....	0.12	1.5/6	25
									Pooled lung	0.31	0.59	0.18	....	0.13		
7	43	Lead and zinc miner	None	?	?	Black	Anthracosis	Anthracosis	Pooled lung	0.43	0.89	0.38	....	0.05	3/2.5	125
8	45	Coal miner	++++	20	5	Black	Anthracosis	Anthracosis	Pooled lung	0.87	0.50	0.43	....	0.44	3/37	8
									Pooled lung	0.71	0.57	0.41	....	0.30		
Group B. Borderline Silicosis and Silicotuberculosis																
9	56	Engineering draftsman	—	38	1	Gray-black	Silicotuberculosis	Tuberculosis	Pooled lung	0.20	0.70	0.14	....	0.06	1/2.5	40
									Pooled lung	0.20	0.73	0.15	....	0.05		
10	27	Lead and zinc miner	—	8 (Safety devices)	1	Gray-black	Tuberculosis	Silicotuberculosis	Pooled lung	0.21	0.94	0.20	....	0.01	1.5/0.5	300
									Pooled lung	0.20	0.93	0.19	....	0.01		
									Hilar lymph nodes	....	....	....	0.55			
11	57	Blacksmith; toolmaker	—	30	1	Black-gray	Silicotuberculosis	Silicotuberculosis	Pooled lung	0.28	0.76	0.21	....	0.07	1.6/4	40
									Pooled lung	0.32	0.70	0.23	....	0.09		
									Hilar lymph nodes	....	....	....	0.70			
									Pancreatic nodes	....	....	....	0.30			
12	56	Holster in lead and zinc mines	++++	16	18	Dark gray	Tuberculosis	Silicotuberculosis	Pooled lung	0.29	0.85	0.24	....	0.05	2/2	100
									Pooled lung	0.28	0.86	0.24	....	0.04		
									Hilar lymph nodes	....	....	....	0.60			
13	41	Chef and copper miner	—	?	?	Gray-black	Fibrocaseous and fibrous tuberculosis	Silicotuberculosis	Pooled lung	0.42	0.78	0.33	....	0.09	2/4	50
									Pooled lung	0.42	0.81	0.34	....	0.08		
									Hilar lymph nodes	....	....	....	0.90			
14	42	Molder in brass foundry	—	6	1	Gray-black	Tuberculosis	Silicotuberculosis	Pooled lung	0.74	0.54	0.41	....	0.33	3/15	20
									Pooled lung	0.76	0.54	0.40	....	0.36		
									Hilar lymph nodes	....	....	....	1.18			

15	60	Molder	—	35	13	Black-gray	Tuberculosis; pneumonoconiosis	Silicotuberculosis	Pooled lung Pooled lung	0.60 0.71	0.83 0.78	0.54 0.55	....	0.11 0.16	3/7	43
16	42	Foundry; coal mines	++++	23	1	Black	Tuberculosis; pneumonoconiosis	Silicotuberculosis	Pooled lung Pooled lung	0.85 0.85	0.65 0.65	0.56 0.56	....	0.29 0.29	4/15	26
							Group C. Uncomplicated Silicosis										
17	35	Millstone sharpener	—	8.5	7	Iron-gray	Silicosis	Silicosis	Pooled lung Spleen Hilus, nodes of spleen	0.65	0.93	0.61	.... 0.16 0.39	0.04	4/2	200
							Group D. Uncomplicated Anthracosilicosis										
18	78	Miner	None	Many	17	Gray-black	Anthracosilicosis	Anthracosilicosis	Lung	1.06 1.05	0.85 0.92	0.91 0.97	....	0.15 0.08	5/6	83
							Group E. Silicotuberculosis (Mixed Silica)										
19	39	Stone-quarry worker	—	9	15	Dark gray	Silicotuberculosis	Silicotuberculosis	Pooled lung Pooled lung Hilar lymph nodes	0.58 0.57	0.60 0.63	0.35 0.36	.... 0.50	0.23 0.21	3/10	30
20	49	Grinder	—	37	1	Dark gray-brown	Silicotuberculosis	Silicotuberculosis	Pooled lung Pooled lung	0.75 0.79	0.83 0.78	0.63 0.62	....	0.12 0.17	4/8	50
21	45	Rock miner	—	18	8	Gray-brown	Silicotuberculosis	Silicotuberculosis	Pooled lung Pooled lung	1.38 1.32	0.74 0.78	1.02 1.04	....	0.36 0.28	8/16	50
22	54	Stonecutter	—	33	1	Gray-brown	Silicotuberculosis	Silicotuberculosis	Pooled lung Pooled lung Hilar lymph nodes Kidney	1.72 1.71	0.70 0.72	1.20 1.23	.... 1.08 0.04	0.52 0.48	10/25	40
23	48	Stonecutter	—	19	4	Gray-brown	Silicotuberculosis	Silicotuberculosis	Pooled lung Pooled lung	3.64 3.59	0.67 0.69	2.47 2.49	....	1.17 1.10	20/50	40
							Group F. Silicotuberculosis (Pure Silica with Incidental Pigment)										
24	29	"Cement worker"	—	0.5	10	Gray-brown	Silicotuberculosis	Silicotuberculosis	Upper part of lung Upper part of lung Lower part of lung Lower part of lung Hilar lymph nodes	0.33 0.34 0.33 0.31	0.88 0.89 0.78 0.84	0.30 0.30 0.26 0.26	.... 0.49	0.03 0.04 0.07 0.05	2,5/1.5	100
25	50	Lead and zinc miner	?	Many	15	Dark gray	Silicotuberculosis	Silicotuberculosis	Left lung Left lung Right lung Right lung Hilar lymph nodes	0.37 0.38 0.35 0.34	0.90 0.87 0.92 0.92	0.33 0.33 0.32 0.31	.... 0.60	0.04 0.05 0.03 0.03	2/2	100
26	33	Lead and zinc miner	++++	17	1	Black and gray	Anthracosilicotuberculosis	Anthracosilicotuberculosis	Pooled lung Pooled lung	0.38 0.38	0.92 0.92	0.35 0.35	....	0.03 0.03	3/1.5	200
27	47	Lead and zinc miner	—	Many	4	Black and gray-black	Anthracosilicotuberculosis	Silicotuberculosis	Pooled lung Hilar lymph nodes	0.37	0.94	0.35	.... 0.36	0.02	3/1	300
28	45	Lead and zinc miner	—	Many	4	Gray-black	Silicotuberculosis	Silicotuberculosis	Pooled lung Hilar lymph nodes	0.41	0.95	0.39	.... 0.58	0.02	3/1	300

TABLE 3.—*Clinical and Pathologic Data and the Results of Analysis for Silica Content of Dried Tissues from Forty Persons with Diseases of the Lungs Caused by Dust—Continued.*

Case	Age, Yrs.	Occupation	Wassermann Reaction	Period of Exposure, Yrs.	Period After Exposure, Yrs.	Color of Lung	Gross Pathologic Condition	Microscopic Pathologic Condition	Tissue Analyzed	Residue in Dry Tissue, %	× Silicon Dioxide Fraction in Residue =	Silicon Dioxide in Dry Tissue, % Lung	Silicon Dioxide in Dry Tissue, % Other Organs	Non-volatile Hydrofluoric Acid Residue, %	Silica Residue Coefficient	Silica Residue Percentage
29	39	Lead and zinc miner	—	14	5.5	Brown-gray	Silicotuberculosis	Silicotuberculosis	Lower part of lung	0.36	0.95	0.34	....	0.02	3/1	300
									Lower part of lung	0.35	0.95	0.33	....	0.02		
									Upper part of lung	0.47	0.98	0.46	....	0.01		
									Upper part of lung	0.50	0.90	0.46	....	0.04		
									Hilar lymph nodes	....	....	....	0.54			
									Bronchopulmonary nodes	....	....	....	0.59			
									Paratracheal nodes	....	....	....	0.34			
30	54	Miner ?	—	..	..	.....	Silicotuberculosis	Silicotuberculosis	Pooled lung	....	....	0.46				
									Hilar lymph nodes	....	....	....	0.45			
31	62	Lead and zinc miner	—	17	7	Black and gray-black	Silicotuberculosis	Silicotuberculosis	Pooled lung	0.67	0.94	0.63	....	0.04	4/2	200
									Pooled lung	0.68	0.98	0.63	....	0.05		
32	37	Lead and zinc miner	—	7	Many	Black and gray-black	Silicotuberculosis	Silicotuberculosis	Pooled lung	0.73	0.95	0.70	....	0.03	6/1.5	400
									Pooled lung	0.75	0.95	0.72	....	0.03		
									Hilar lymph nodes	....	....	....	0.80			
33	65	Lead and zinc miner	—	40	4	Black and gray-black	Silicotuberculosis	Silicotuberculosis	Pooled lung	0.95	0.94	0.90	....	0.05	5/2.5	200
34	55	Lead and zinc miner	—	33	2	Black and gray-black	Silicotuberculosis	Silicotuberculosis	Pigmented area	1.24	0.91	1.13	....	0.11	10/5	200
									Pneumonic area	0.18	0.94	0.17	....	0.01		
									Pneumonic area	0.17	0.92	0.16	....	0.01		
35	48	Lead and zinc miner	—	?	5	Black and gray-black	Silicotuberculosis	Silicotuberculosis	Pooled lung	1.62	0.97	1.57	....	0.05	12/2	600
									Pooled lung	1.61	0.97	1.57	....	0.04		
							Group G. Siderosilicotuberculosis									
36	76	Iron miner	None	50	2	Brown	Siderosilicotuberculosis	Siderosilicotuberculosis	Pooled lung	....	....	0.64				
37	..	Iron miner	None	..	..	Brown	Siderosilicotuberculosis	Siderosilicotuberculosis	Pooled lung	....	....	0.68				
38	..	Iron miner	None	..	..	Brown	Siderosilicotuberculosis	Siderosilicotuberculosis	Pooled lung	....	....	0.73				
							Group H. Anthracosilicotuberculosis									
39	58	Lead and zinc miner	—	15	20	Black and gray-black	Anthracosilicotuberculosis	Anthracosilicotuberculosis	Pigmented lung	0.60	0.69	0.41	....	0.19	3/8	37
									Pigmented lung	0.60	0.69	0.41	....	0.19		
									Nonpigmented lung	0.58	0.88	0.51	....	0.07		
									Nonpigmented lung	0.65	0.76	0.50	....	0.15		
40	45	Coal and zinc miner	—	11 and 18	Several	Black and gray-black	Anthracosilicotuberculosis	Anthracosilicotuberculosis	Pigmented lung	1.78	0.83	1.48	....	0.30	10/10	100
									Pigmented lung	1.83	0.84	1.55	....	0.28		
									Nonpigmented lung	1.23	0.91	1.12	....	0.11		
									Hilar lymph nodes	....	....	....	0.43			

The number of milligrams per gram of dry tissue may be obtained by multiplying the percentage of silicon dioxide in the dried tissue by the [illegible]

CASE 1.—A resident of Chicago, aged 29, had spent five and a half years as a machine worker in a room in which asbestos was handled and in which the air was reputed to contain much dust. All the results of examination were characteristic of an advanced stage of pulmonary tuberculosis, but the silica content of each lung and of the hilar lymph nodes was smaller than we have ever found. Two different samples were analyzed in triplicate from various portions of the lung; so the results are without any doubt reasonably correct. There is no explanation of these low values at present.

CASE 2.—A Finnish-American, aged 34, had worked "several years in the copper mines of Michigan." He had not been in the mines for seven years. Even with this history there was a silica content of only half the normal value. The disease was typical tuberculosis.

CASE 3.—A Danish man, aged 27, had worked as a machinist for eleven years. The observations were characteristic of pulmonary tuberculosis. Examination, however, showed a dense fibrous cap on the posterior aspect of the upper lobe of each lung. The cut surfaces of the consolidations were iron-gray and offered considerable resistance to the knife. There were calcifications in these masses. Microscopically they were composed of fibrotic whorls, which were undergoing various degrees of caseation. Chemically the silica content was 1.5 mg. per gram of dried lung, a quantity only slightly above the normal for a person of the patient's age. There may have been enough silica present to aggravate the tuberculosis. If everything is taken into consideration, it seems clear that the silicosis was an incident of little consequence in this case.

CASE 4.—A man, aged 60, was a boiler maker in the lead and zinc mines. He had not been in the mines for many years. On June 7, 1934, he stated that for the past six weeks he had had pain in the anterior part of the right side of the chest. He also complained of having had asthma for the past six years, with cough and little expectoration for many years. One day prior to consultation he spat a small amount of blood. The laboratory findings were normal.

There were cancer of the upper lobe of the right lung, with metastases throughout the body; marked pneumonoconiosis (anthracosis); marked bilateral bullous emphysema; slight tubular bronchiectasis; terminal bronchopneumonia on the right side, and an old primary tubercle in the hilar lymph nodes, with ancient fibroid tuberculosis in the upper lobe of the right lung.

There were a large amount of coal pigment, emphysema and slight bronchiectasis, but no silicosis. The silica content of the left lung was normal (1.5 mg. per gram), and that of the right, only 0.7 mg. The nonvolatile hydrofluoric acid residue of the left lung was 3.5 mg. per gram (nineteen times the normal amount), showing that there was an accumulation of material resulting from the patient's occupation. The low value for the right lung was due to the dilution of silica by the action of the new growth and the terminal bronchopneumonia. The lung was damaged, owing to the long exposure to dust, but the process was simple pneumonoconiosis and not silicosis.

CASE 5.—A German-American aged 64, a janitor for forty-five years, had had a cough with expectoration for twenty years. There had been one doubtful report of tubercle bacilli in the sputum. At no time did we find tubercle bacilli. The pathologico-anatomic diagnosis was as follows: bilateral disseminated bronchiec-

tasis; emphysema; anthracosis; fibrous obliterative pleuritis on the right side; cloudy swelling of the myocardium; passive congestion of the liver; amyloidosis of the kidney, adrenals and spleen; trophic ulcers over both tibias; indirect inguinal hernia on the left side, and pernicious anemia.

The silica content was within normal limits, and the nonvolatile residue was one-half the silica content. The appearance was definitely that of mild pneumonoconiosis due to coal dust, which no doubt aggravated the bronchial infection and bronchiectasis. Even so, the patient lived beyond his normal life expectancy.

Case 6.—A molder, aged 59, had a condition which was clinically diagnosed as asthma. Roentgenographic examination showed marked infiltration throughout the lungs, which was probably silicosis. The pathologic diagnosis was bronchopneumonia, passive congestion, emphysema and bronchiectasis.

Terminal bronchopneumonia is the principal immediate cause of death of foundry workers, according to McConnell and Fehnel,[34] who stated that the death rate for molders due to this disease is two and one-third times the normal rate. The silica content of 1.8 mg. (without dilution) was within the normal range. The amount of nonvolatile residue was six times the normal value, indicating dust other than silicon dioxide.

Case 7.—A lead and zinc miner, aged 43, from the southeastern part of Missouri, died of gastric hemorrhage before an accurate history was obtained. Apparently there had been no pulmonary complaint. From the results of examination of the specimen of lung it was evident that there had been contact with carbon and silica. The lung was black, with considerable fibrosis and emphysema. Small dense foci of black pigment were scattered throughout the tissue. The lymph nodes were from 2 to 3 cm. in diameter and were black. They did not appear silicotic.

Sections from a hilar lymph node revealed almost solid masses of phagocytosed black pigment throughout the node, with a few regenerated follicles of lymphoid tissues; there was also typical congestion of all the lymph vessels with phagocytosed black pigment (fig. 1 *a* and *b*).

In the larger foci there was a moderate amount of linear fibrosis. Marked emphysema was also present. At no place was there any suggestion of characteristic fibrotic whorls. Even the early accumulation of fibroblasts was not present.

The silica content of 3.4 mg. (without dilution), however, reveals that the patient had been exposed to silica either as a hard coal miner or as a worker in the lead and zinc mines. The condition was a prefibrotic stage of silicosis.

Case 8.—A Pole, aged 45, had been a coal miner for twenty years. He had had a cough with pain in the chest and dyspnea for fifteen years. The Wassermann reaction was positive.

There was thrombosis of the pulmonary artery to the right upper and middle lobes and of one branch to the left upper lobe. In the apex of the right lung was seen a small apparently tuberculous cavity. There were consolidation of the lower part of the upper lobe of the right lung and necrosis with the formation of cavities.

34. McConnell, W. J., and Fehnel, J. W.: J. Indust. Hyg. **16**:227, 1934.

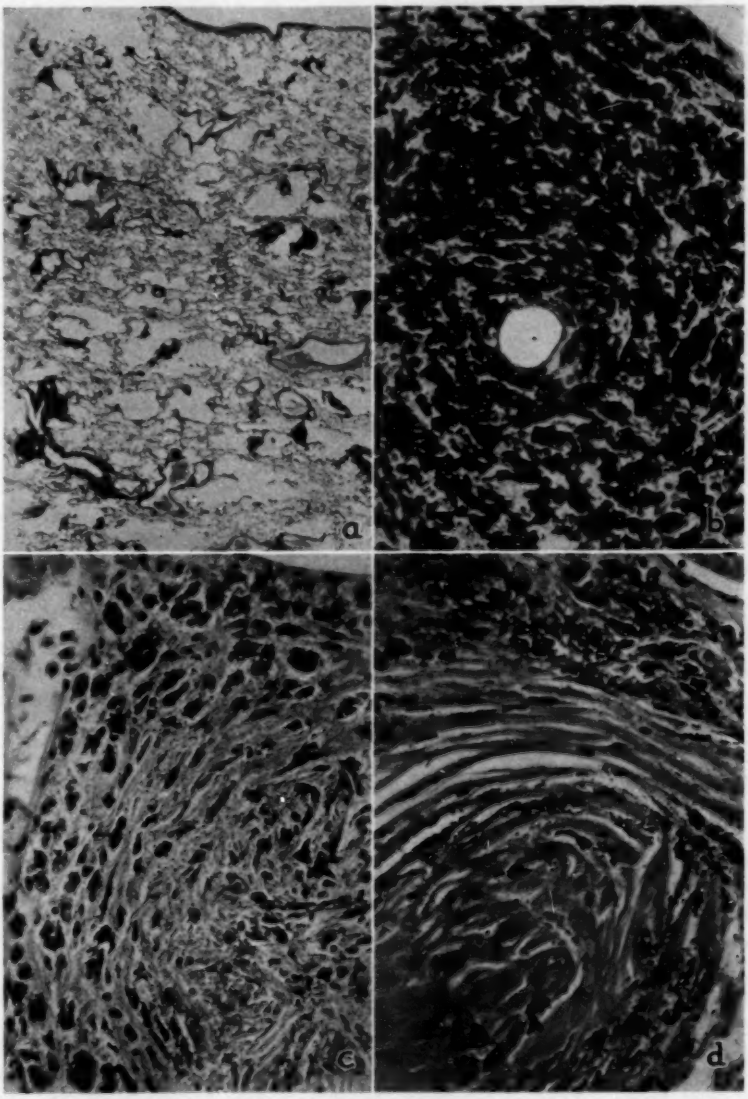

Fig. 1.—Photomicrographs: *a*, low magnification (× 5) of a section of the lung of a man who had worked in coal and lead and zinc mines (case 7), showing blocking of the lymphatics by pigment; *b*, high magnification (× 320) of a portion of the section shown in *a*, revealing the lack of fibrous tissue; (*c*) high magnification (× 120) of a section from a similar nodule in the lung of a lead and zinc miner (case 28), in which there is laying down of fibroblast around a central core, and *d*, the same magnification (× 120) of a section from the same nodule from which the tissue photographed in *c* was taken, showing the completed fibrous whorl. Hematoxylin-eosin stain.

In the anterior part of the lobe was marked reddish infiltration characteristic of bronchopneumonia. Dense, even distribution of coal pigment was seen throughout. There was no calcification of the hilus. Throughout the upper lobes and especially the bases of both lungs there was rather marked fusiform dilatation of all the terminal bronchi.

Some of the microscopic sections revealed large bronchiectatic dilatations with thickened mucosa. The surrounding tissue contained large amounts of black pigment. There was an extreme degree of emphysema and bronchiectasis. The lymphatic vessels and lymph follicles were packed with phagocytes containing black pigment. The alveolar walls were interspersed throughout with black pigment. There seemed to be complete obliteration of the lymph spaces. There was definite pneumonic infiltration in one section, setting off numerous islands of irregular foci of black pigment. The lymph nodes at the hilus were also packed with coal pigment.

The silica content was more than twice the normal, with little dilution, while the amount of the nonvolatile hydrofluoric acid residue was seventeen times the normal value. The relationship of these two ratios is a valuable aid in determining the type of work in which the patient has been engaged, as will be shown later.

Nothing could demonstrate pure "anthracosis" better than this specimen. There were the history, the characteristic roentgenogram, the black lung, the engorgements of the lymphatics with coal pigment (free and in the phagocytes), the lingering bronchitis resulting in bronchiectasis, the disability, the quiescent tuberculous focus and, finally, the terminal pneumonia.

GROUP *B.—Patients with borderline silicosis and silicotuberculosis.*

CASE 9.—An Englishman, aged 56, had worked as an engineering draftsman all his life. He had characteristic pulmonary tuberculosis.

There was a dense black fibrous cap covering the upper lobe and a few scattered fibrous nodules throughout the upper half of each lung. There were five or six small cavities in the upper lobe of the left lung and also in the apexes of both lower lobes. Otherwise the appearance was characteristic of pulmonary tuberculosis.

The chemical finding of 1.4 mg. of silica per gram of dried lung was slightly above the normal level if the degree of dilution is considered.

The case is unusual in that the changes were nearly all in the apex or the upper third of the lung, contrary to the classic conception of silicosis. It reveals the effect of tuberculosis on this disease. The more tuberculosis a patient has the greater is the tendency of the disease to appear in the upper part of the lungs.

CASE 10.—A lead and zinc miner, aged 27, who had worked for eight years in the mines, in which safety devices were used, had a history of typical pulmonary tuberculosis. There was 1.9 mg. of silica per gram of dry lung.

CASE 11.—A Scotch blacksmith and tool maker, aged 57, suffered from a condition which began with a hemorrhage and resembled tuberculosis. The right lung was adherent throughout. The left lung was free, but the surface was entirely

black, especially that of the anterior part and the upper portion of it. The lymph nodes were black and contained "shells of calcification." On the right side of the mediastinum was a large chain of the black calcified nodes, extending to the diaphragm, which had the gridiron-like appearance characteristic of silicotuberculosis rather than that of ordinary tuberculous calcification (fig. 2 *a*). In the upper lobe of the right lung were numerous oblong, recently excavated cavities forming in fibrocaseous consolidations. There were large tuberculous masses throughout, some of which contained a large amount of black pigment. In the base of the right lung scattered black nodules, from 1 to 3 mm. in diameter, occurred in markedly emphysematous lung tissue. On the left side were a few small, recently ulcerated cavities, with scattered black nodules, such as have been described in the base of the right lung. Some of these were very small. There were several cavities in the lingula. On the anterior wall of the esophagus just below the bifurcation of the trachea was a pouch, measuring 8 by 5 mm. and 4 mm. deep the bottom of which was firmly adherent to the hard, enlarged tracheobronchial lymph nodes. The adherent portion contained a black deposit in the submucosa, which was exposed in a circular area of erosion 3 mm. in diameter. Three centimeters above this area was a similar pinkish-gray pouch, only 2 mm. deep and not related to the lymph nodes. There was also tuberculous prostatitis.

Sections from a bronchial lymph node revealed only occasional islands of lymphocytes. The tissue was replaced by dense, eosinophilic hyaline connective tissue, some of which was arranged in nodular whorls. Numerous clefts were seen throughout, containing black pigment in granules. At the periphery the pigment was observed in large polygonal cells.

There were many foci of calcification throughout. Low magnification revealed a dense hyalinized capsule of connective tissue and islands of the same substance throughout the node, surrounded by angular regions of black pigment, which varied in its intensity from one place to another. With higher magnification these islands of connective tissue appeared in whorls, some intact, some thinned in early stages of homogeneous caseation and some adjoining the black areas with smooth, chopped-off borders or presenting gnawed-out indentations (fig. 2 *b* and *d*). In the larger mass of old silicotic nodules could be seen the open dagger-like spaces left by dissolved fatty acid and cholesterol crystals. The picture suggests that these crystals resulted from caseation, which in this case (and in most other instances) is due to collateral tuberculosis. Around these areas could also be seen the early formation of the blue-staining hollow spheres of calcium soaps and insoluble calcium salts formed in earlier stages of calcification (fig. 2 *c*, *e* and *f*). It is our opinion that in cases of silicosis such a formation represents a collateral infection, chiefly by the tubercle bacillus. The reasons for this belief are that in the advanced, old silicotic nodule studied in case 17 there was no caseation, calcification or deposition of "fat" crystals. Another indication is that in certain lymph nodes the caseation and calcification take place first around the borders of the node, suggesting that the tuberculous infection becomes active and advances around the margins after the older silicotic nodules have been formed. In many of the nodules could be seen a compact whorl with gradual shading off around the margins until typical tuberculous caseation occurred. In this instance the two processes had apparently run parallel in some places, while in others tuberculosis dominated. The black regions around the old silicotic nodules were made up of coal or iron pigment (or both). Much of the pigment was free, sometimes in large masses; some was in little "sarcophagi" of old autolyzed phagocytes, while some was still inside the phagocytes. No active phagocytic cells were observed. The liberated autolytic enzymes apparently digested much tissue,

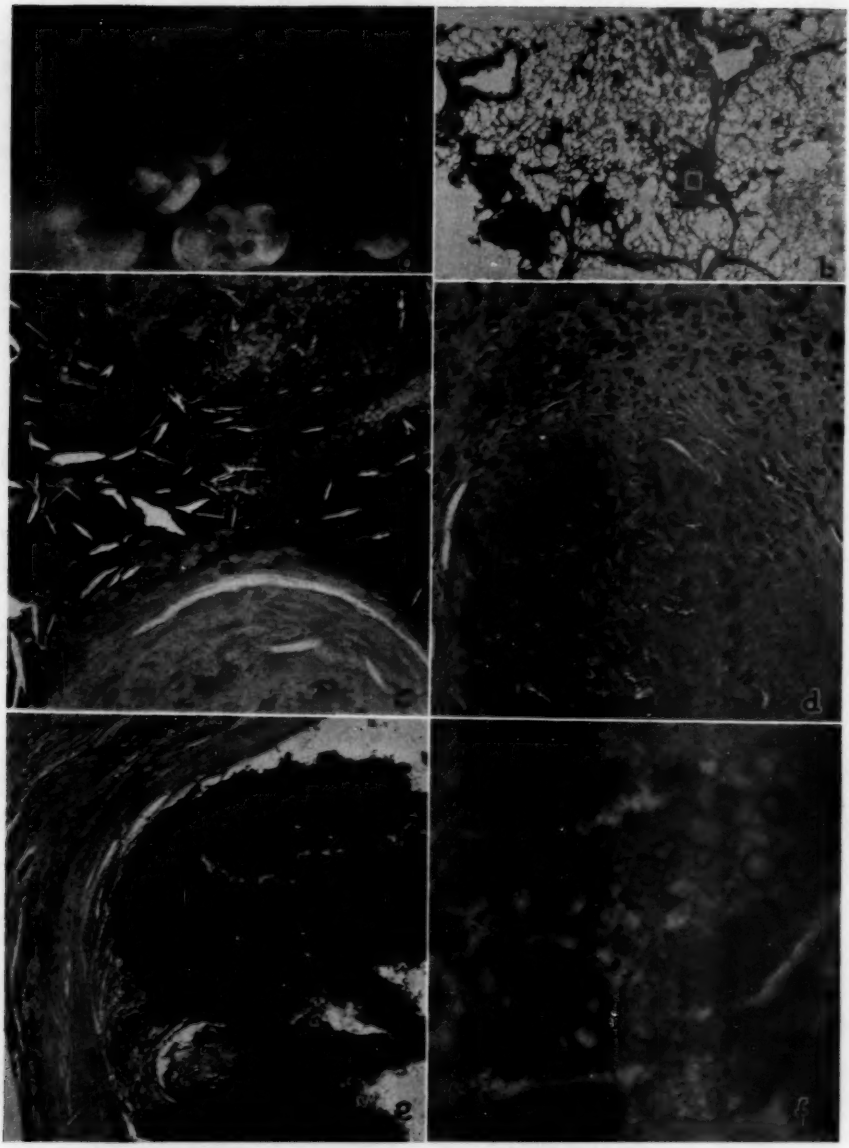

Fig. 2.—In *a* is shown a roentgenogram of the hilar lymph nodes in case 11, revealing calcification of the "egg-shell" type. The left main bronchus is shown in the upper portion of the field at the right. Photomicrographs: *b*, with low magnification of a section (× 4) in the same case as that in which the lymph nodes shown in *a* occurred, revealing silicotic nodules and silicotic tubercles; *c*, of a section (× 100) of silicotic nodules taken from a lymph node shown in *a*, which are undergoing caseous and calcareous degeneration; *d*, of the portion of the field indicated in *b* (× 100); *e*, of a portion of a node shown in *a* (× 70), revealing a focus of calcification, and *f*, of calcareous globules occurring in the silicotic nodules shown in *c* (× 900). Hematoxylin-eosin stain.

leaving irregular islands of undigested tissue. This adds weight to the theory that ulceration may occur without infection, although it rarely has an opportunity because of infection that acts much faster. The lung revealed transition of nodules from those of the silicotic type to typical caseous tubercles. The most characteristic of the silicotic nodules will be described.

With a magnification of 10 diameters there were observed individual and conglomerate pink-staining masses from 1 to 3 mm. in diameter (actual size), revealing concentric rings in some of the isolated masses but amorphous centers in the larger ones. In all the masses there were rows of brown and black pigment along the seams between the nodules and between the fibers in the nodules. Around these pink nodules was tissue which stained dark blue. With higher magnification the pink nodules were observed to be typical tuberculosilicotic nodules undergoing varying degrees of caseation but no calcification. The brown pigment was contained in phagocytes, which were monocytic cells of the "alveolar" type. There were many of these cells without any pigment and many lymphocytes, as well as scattered Langhans giant cells and true miliary tubercles. It was believed that the process had gone on as mild silicosis or silicotuberculosis for a long time, finally veering more and more toward true tuberculosis. The other sections revealed increasingly marked tuberculosis as the tuberculous lesions at the apex were approached, all trace of a silicotic character finally being lost.

There was 2.4 mg. of silica per gram of dried lung and 7 mg. per gram of the lymph nodes. There was perhaps considerable dilution, due to the tuberculosis.

This case represents the first stage of silicosis, dampened by anthracosis on the one hand and aggravated by tuberculosis on the other. Because the reaction in the lymph nodes was only that observed in cases of silicotuberculosis, with or without anthracosis, it must be conceded that the silicosis, even though the silica content was small, was a definite factor in the development of the fatal tuberculosis. This type of involvement of the lymph nodes is peculiar to slowly progressive tuberculosis when superimposed on silicosis. It is revealed also that there may not be much relation between the silica content and the extent of the disease. Even if allowance is made for dilution by the action of inflammatory tissue, there is still a low silica content. The relation between the time of exposure and the amount of silica in the lungs can at present not definitely be determined by chemical analysis.

CASE 12.—An American, aged 56, had worked for sixteen years as a hoister and shaft sinker in the lead and zinc mines of the Ozark region. He had been a barber for seventeen years before his death and had been infected with syphilis sixteen years prior to his death.

This case proved to be one in which there was minimal silicosis complicated by ordinary pulmonary tuberculosis and syphilis. The silicosis played little or no rôle in the tuberculosis, because the tuberculosis began in the subapical region, with no activity in the foci of silicosis until late in the process.

CASE 14.—An Armenian, aged 42, had spent six years as a molder in a brass-foundry. In every way the disease appeared to be pulmonary tuberculosis. At postmortem examination tuberculosis was observed, with a considerable amount of black pigment. The microscopic examination, however, revealed a few whorls characteristic of silicosis, which were undergoing tuberculous caseation. The

chemical content (4 mg. per gram of dried lung) was sufficiently high to indicate silicosis, but the significance of the other findings was rather doubtful. It is questionable how much the silica aggravated the tuberculosis.

CASE 15.—An Austrian, aged 60, had worked as a molder for thirty-five years but had not been in this work for thirteen years. He gave a rather typical history of pulmonary tuberculosis. The lung contained coal pigment throughout to a marked degree. The pleura was almost entirely black. There was a large cavity in the upper lobe of the right lung, which extended through the septum and into the lower lobe. There were a few cavities in the upper lobe of the left lung. Many acinonodose tubercles were present throughout the whole lower and middle lobes. There was nothing to suggest silicosis.

The sections of lymph nodes from the hilus revealed masses of phagocytes filled with coal dust and some autolysis, leaving crevices in the tissue. There were new accumulations of lymphoid tissue around the border. Occasional patches of hyalinized fibrous tissue occurred throughout but not in whorl formation. Sections from different parts of the left lung and from the base of the right lung revealed a peculiar type of fibrosis with more recent overlapping tuberculosis. The tissue contained much more silica than the other observations would lead one to expect. The perivascular lymphatics were packed with black and brown pigment, both free and in cells. Some of the masses were from 2 to 7 mm. in diameter, and some were in confluent masses 1 cm. in diameter. They were rarely circumscribed like a typical silicotic nodule but were irregular masses of phagocytes that had originally filled the lymphatics to overflowing.

There was 2.4 mg. of silica per gram of dried lung, a content definitely higher than the normal.

The clinical, roentgenographic and gross pathologic examinations revealed only an advanced stage of tuberculosis, chiefly unilateral, with coal pigment, while the microscopic examination showed that the centers of the pigmented masses had undergone marked fibrosis. This fibrosis was not at all like that usually observed in the whorls occurring in silicosis but was wavy, bulbous and irregular. The nodules were rarely round. Usually they were irregular in size, arrangement and density. Only occasionally did they show a tendency to become round, and then only when a tuberculous process was present. Except for the history and the results of microscopic examination and chemical analysis, there was no indication of silicosis.

GROUP *C.—Patients with apparently uncomplicated silicosis.*

CASE 17.—A Bohemian, aged 35, had been a millstone sharpener in flour-mills for eight and one-half years but had not been in this occupation for seven years. In 1916 he underwent a tonsillectomy, which was followed by a severe cough, like that associated with an advanced stage of pulmonary tuberculosis, and a loss of 40 pounds (18.1 Kg.) in weight. He was admitted to the hospital on Jan. 16, 1924, with a diagnosis of advanced tuberculosis, but except for dyspnea on exercise he was well and comfortable. The laboratory findings were normal, but the roentgenographic examination revealed what was later observed to be the third stage of silicosis, in which all the lesions in the upper three fourths of the lung had become confluent and presented a dense shadow, representing a solid mass of fibrous

tissue. The bases of both lungs were emphysematous. The patient contracted a "cold" and died in a few hours of minimal bronchopneumonia.

The left lung weighed 1,200 Gm. and was firmly bound to the pleural wall. It was removed from the thorax in a solid boardlike mass. There was no pus or caseation. On external appearance the lung could be divided into halves by a horizontal plane near the middle. The upper half was dome-shaped and was covered by the adherent parietal pleura as though by a mantle (fig. 3 *a*). The lower half was suspended below this plane like a pendulum. The upper half was solid and uncompressible. The lower half was spongy, semisolid and crepitant near the lower border. The lingula was retracted and contained many firm nodules. There were several large, black, almost cartilage-like lymph nodes near the hilus. Scraping the knife over the surface produced a sensation of grating. On vertical section through the midaxillary line, the lung was again divided into two zones—one, extending from slightly below the hilus to the apex, was composed of an iron-

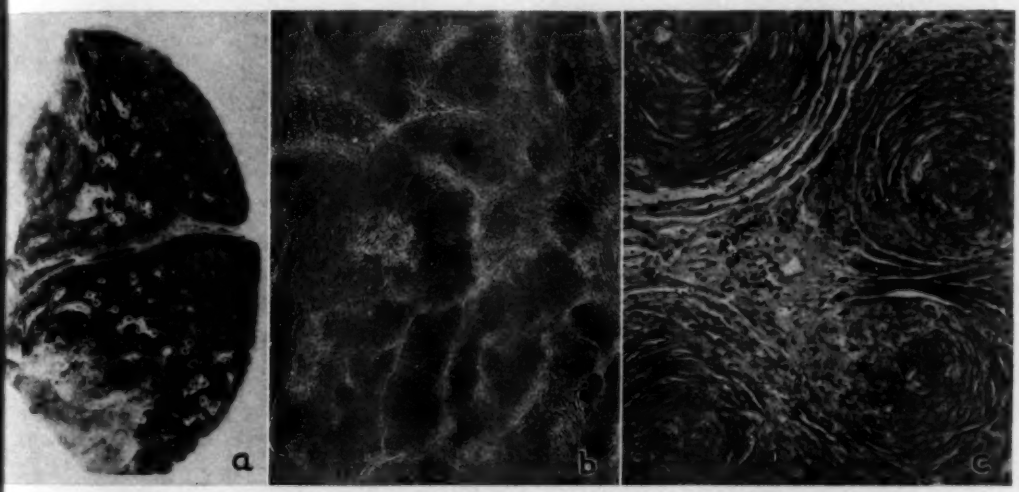

Fig. 3.—In *a* is shown a photograph of a sagittal section of the lung in case 17, revealing complete fibrous consolidation of the upper nine tenths of the lung; in *b*, a low power photomicrograph (× 11) of tissue from the lung the gross photograph of which appears in *a*, and in *c*, a high power photomicrograph (× 90) of the section shown in *b*, revealing pure fibrosis without any caseation or calcification and with practically no pigment.

gray solid substance with a yellowish cast. This cut with marked resistance; in fact, the knife grated through it. The surface was uncompressible, and the only breaks noticed were at the openings of the vessels and bronchi. Many blood vessels and bronchi were smaller than normal, a large number of which were almost completely obliterated. The lower zone was pinkish red on the upper border and dark red below. There were many small hemorrhagic patches about 9 mm. in diameter throughout the lower part of the lung. The right lung weighed 1,200 Gm. and was otherwise similar to the left. There was a large lymph node at the hilus, measuring 5 by 4 by 3 cm., having the same consistency as that of the lung. The cut surface had the same grayish-yellow appearance, and the lung cut with more resistance.

The spleen weighed 250 Gm.; it was bluish red and of normal consistency. There was much fibrosis. There were several large firm nodes at the hilus, measuring 2 by 3 by 4 cm., which were slate-gray and resembled the nodes at the hilus of the lung.

The heart weighed 360 Gm. The right ventricle was preponderant, and the wall measured 6 mm. in thickness. The tricuspid valve admitted four fingers easily. The musculature was red and free from scars.

Numerous sections of the tissue of the lung revealed solid confluent whorls of typical silicotic nodules (fig. 3 *b* and *c*). In the centers they contained a few disintegrated phagocytes. Around the borders a few lymphocytes and some pigment were seen. There was no caseation or evidence of tuberculosis in this specimen. The blood vessels were markedly constricted and few. The changes in the hilar lymph nodes were essentially similar to those in the lung. Some had small areas of normal lymphoid tissue, but most of them were packed solid with silicotic whorls. The base of the lung showed characteristic bronchopneumonic exudation along the lower border of the silicotic consolidation. This case appeared to be an instance of uncomplicated silicosis. The lymph nodes at the hilus of the spleen and along the esophagus, extending through the diaphragm, showed similar silicotic whorls. There were no nodules characteristic of silicosis in the spleen, however.

Chemical analysis revealed 6.1 mg. of silicon dioxide per gram of dried lung tissue; the lymph nodes at the hilus of the spleen contained 4 mg. per gram, and the spleen itself, 1.7 mg.—a much higher content than that of the normal spleen. The extent of the involvement with silicosis and its apparent freedom from associated infection seem unique.

Although such massive involvement is not thought to be possible without infection, it was certainly free from tuberculous infection. The case affords an example of massive involvement without ulceration. The question arises at this point whether ulceration can occur without infection. When extensive phagocytosis of coal dust or toxic silica or both is continually going on, there is apparently liberation of sufficient enzyme to digest fibrous tissue. The work of Opie[35] on the enzymes of blood elements was in support of this observation.

For involvement of the type present in this case, the silica content (6.1 mg. per gram) was not excessive. In this connection it must be pointed out that the quantity of silica is not the only factor of importance. In addition to the silica content it is essential to know the form in which the silica is present and the size of the particles. A high content of silica may be due to relatively harmless silicates or to particles too large to go into solution. What is really important, as expressed by Haldane,[36] is the silica that has been taken in and then dissolved. It is the silica no longer present rather than the silica present that has done the damage, although one must not assume that all the dissolved silica is detrimental.

35. Opie, E. L.: Physiol. Rev. **2**:552, 1922.

36. Haldane, J. S.: Colliery Guardian, 1934, pp. 148, 341, 540 and 582.

The appearance of the heart was characteristic of that seen in an advanced stage of silicosis. There was enlargement of the right ventricle due to reduction of the average diameter of the vessels of the lesser circulation.

GROUP *D.—Patients with uncomplicated anthracosilicosis.*

CASE 18.—A man, aged 78, dropped dead, owing to rupture of the right ventricle. The whole picture was that of mild silicosis, modified by the presence of a slight amount of coal pigment with a very early stage of tuberculous infection—too early, in fact, to cause any caseation except in one or two isolated tubercles (fig. 4 *a* and *b*). The case illustrates the cardiac damage that results in silicosis. Owing to endarteritis the pulmonary vessels are destroyed, and a tremendous burden is placed on the right side of the heart.

GROUP *E.—Patients with silicotuberculosis.*

CASE 20.—A knife grinder from Sheffield (England), aged 49, who had worked as such for thirty-seven years, had pulmonary tuberculosis.

The microscopic appearance was that of silicotuberculosis. One of the interesting features was the atypical position of the silicotic involvement along the subapical bronchi in the upper lobes. Another feature was a terminal abscess of the lungs due to the colon bacillus.

CASE 21.—A Jugoslav, aged 45, had worked for eighteen years as a rock miner but had not been in the mines for eight years before his death. He entered the hospital with pulmonary tuberculosis.

The lungs were large and contained a marked amount of coal pigment. There were numerous large, hard, slate-gray and yellow-gray nodules throughout the middle portions of both lungs and some toward the apexes. The main lymph nodes occurring from the hilus along the bronchi were enlarged and gray-black with streaks of yellow. The roentgenogram taken post mortem revealed the typical egg-shell calcification so common in cases of silicotuberculosis. Some of these nodes were dense and calcareous, and some of the nodules toward the base showed signs of softening. A tuberculous infection seemed to be superimposed on an advanced stage of silicosis. The heart weighed 400 Gm., and the right ventricle was large, with a wall 9 mm. in thickness.

Microscopically the hilar lymph nodes contained solid masses of ancient whorls of fibrous tissue typical of those occurring in silicosis. There was also calcification, particularly around the borders, characteristic of silicotuberculosis. These lymph nodes appeared on the roentgenogram as gridlike formations. The massive nodules in the parenchyma were made up of fibrotic whorls containing much pigment, especially around the periphery, and some of these were undergoing caseation (fig. 4 *c*).

CASE 22.—An Italian-Swiss stone carver, aged 54, who had worked at this trade for thirty-three years, entered the hospital with rather typical pulmonary tuberculosis.

The upper part of the right lung contained a huge cavity with a thick wall. There was a cavity in the middle of the left upper lobe. Around the hilus and extending into the parenchyma of the lung to the pleura were grayish-black nodular masses, characteristic of silicosis, mixed with fibroid and fibro-ulcerative tuberculosis. There were irregular scattered nodules toward the apexes and the bases of both lungs. There were large calcifications on the right of the trachea, the

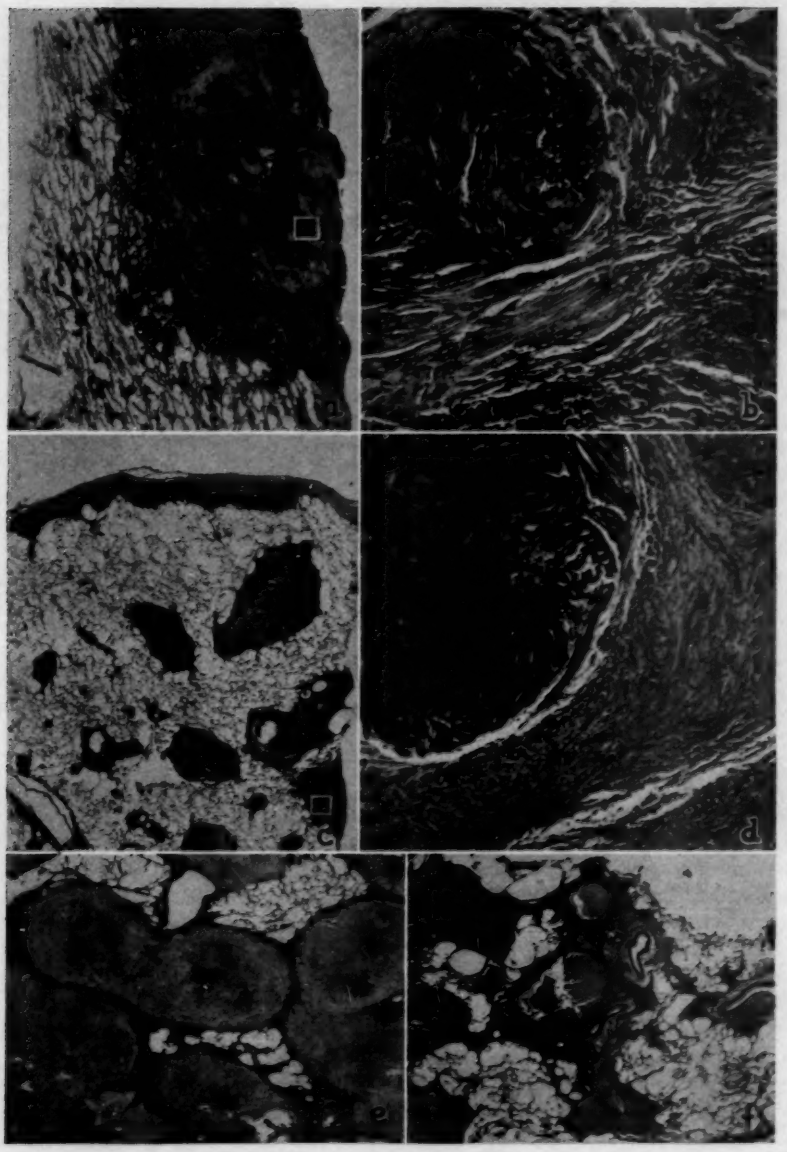

Fig. 4.—Photomicrographs: *a*, low magnification (× 4) of the lung of a miner aged 78 (case 18), revealing masses of silicotic fibrosis and only a few foci of tuberculosis; *b*, high magnification (× 110) of the section indicated in the small square in *a*; *c*, low magnification (× 4) of tissue in case 30, showing silicotic nodules with a gradually widening zone of tuberculosis; *d*, high magnification (× 110) of a portion of the same field as that shown in *c*, illustrating the change in the fibrous tissue at a distance from the central core of silicotic fibrosis; *e*, low magnification (× 5) of a section of homogeneous tuberculous silicotic nodules in the lung of a rock miner (case 21), showing the slurring of the fibers, and *f*, low magnification (× 5) of a section of the lung of a stonecutter (case 22), showing caseation of tuberculous silicotic nodules (the tuberculosis is gaining the ascendency). Hematoxylin-eosin stain.

largest measuring 1.5 by 2 by 4 cm. These were strictly of a primary tuberculous nature and were not due to silicotuberculosis. The heart weighed 365 Gm., and the wall of the right ventricle measured 8 mm. in thickness.

The lymph nodes at the hilus and the bronchopulmonary nodes were similar to those described in case 21 (fig. 4*f*).

The silica content of the lung was 14 mg. per gram, and that of the hilar nodes, 10.8 mg. per gram. The kidney, which was normal, contained only 0.4 mg. per gram.

GROUP *F.—Patients with silicotuberculosis (pure silica with incidental pigment).*

CASE 24.—An American, aged 29, had worked for six months, ten years before his death, in a cement factory in LaSalle, Ill. On his admission to the hospital the diagnosis was pulmonary tuberculosis.

The upper portion of each lung contained shrunken fibrous cavities with dense fibrous caps from 1 to 2 cm. in thickness. In the middle portion of each lung were numerous small slate-gray nodules, some of which were caseous, from 2 to 3 mm. in diameter. Toward the base the nodules were small and few. At the bifurcation at the hilus, the lymph nodes were greatly enlarged, tough and fibrous, with a slate-gray color characteristic of silicosis (fig. 5*a* and *b*). The heart weighed 455 Gm. The right ventricle was dilated and the wall was 7 mm. in thickness.

The silica content was relatively low in both the parenchyma (3 and 2.6 mg. per gram) and the lymph nodes (4.9 mg. per gram). The striking fact in this case is the short exposure (six months).

If the observations in this case are true, as they seem to be, there still is much to learn regarding silicosis and silicotuberculosis. The results in this case are comparable to those in Kettle's [37] experiments on animals with exposure to clay and tubercle bacilli, in regard to the rapidity of formation and the end-results. The heart showed a picture characteristic of an advanced stage of silicosis.

CASE 26.—An American, aged 33, had worked for seventeen years as a lead and zinc miner at Picher, Okla. The Wassermann reaction was 4 plus, and there was a typical history of pulmonary tuberculosis. The observations on physical examination were characteristic of silicotuberculosis, perhaps aggravated by syphilis. The large "egg-shell" type of calcified lymph nodes was characteristic of silicotuberculosis.

CASE 27.—A man, aged 47, had been a lead and zinc miner for many years. Roentgenograms taken on Oct. 17 and Dec. 1, 1933, were essentially similar. There was an increase in the arborization from the hilus in the base of the lung. The hilus was thickened on each side, but more on the right. Along the linear striations (or arborizations) were observed a few fine areas of increased density, which could in no way be considered as nodules. In the apex of the lower lobe of the left lung was an area of greater density 1.5 cm. in diameter, appearing like a calcified tubercle. In the right hilus were several large areas of increased density. In the right upper lobe, extending from the hilus, was a large round mass, sharply circumscribed and appearing to be a contracted upper lobe. It measured about 8 by

37. Kettle, E. H.: J. Indust. Hyg. **8**:491, 1926.

12 cm. A roentgenogram taken on July 11, 1934, showed extension of this mass toward the base, with an irregular border at this time. It appeared to be cancer of the lung.

The right lung was contracted to one-half the normal volume, and a heavy layer of fibrous adhesions covered the dome and a thinner layer the base, which was

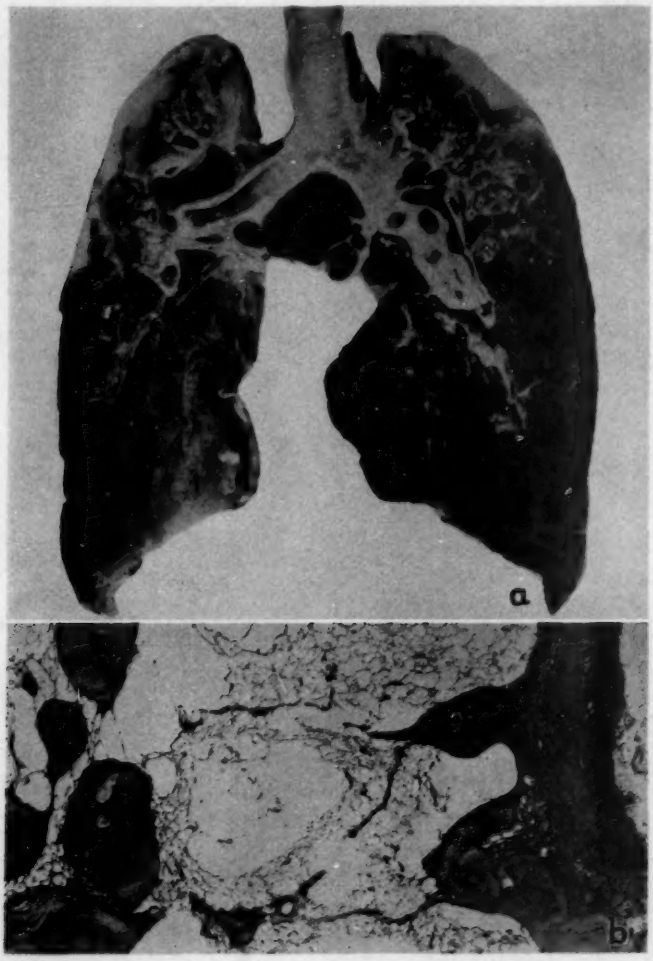

Fig. 5.—In *a* is shown a sagittal section of the lung of a cement worker exposed for six months (case 24), and in *b*, a low power photomicrograph (× 5) of tissue from the same lung as that shown in *a*, revealing tuberculous silicotic nodules in the parenchyma and beneath the pleura. Hematoxylin-eosin stain.

grayish-black. The left lung was covered with patches of black tissue, alternating with areas of pink-gray, more black substance being present in the upper part than over the base. On section through the right lung a huge solid black mass appeared, which filled the greater part of the base of the upper lobe. The mass was black

with areas of gray; it was firm but softened when touched, and it was resistant to section with a knife. It measured 7 cm. in diameter. Throughout the middle and lower lobes were irregular masses of consolidation, ranging from dark gray to yellow-gray—the more yellow the appearance, the greater the softening. Some of these areas contained cavities. In the left lung there was a large tuberculous mass 1.5 cm. in diameter at the apex of the lower lobe, containing areas of fibrosis and dry caseous material. Various similar but smaller masses were scattered throughout the lung. In the middle section were numerous small gray-black nodules, from 1 to 1.5 mm. in diameter. A partially calcified lymph node complex, corresponding to a tuberculous silicotic mass, occurred in the apex of the lower lobe of the left lung.

The silica content of mixed samples of the lung was 4.2 mg. per gram, and that of the silicotic tuberculous mass in the right upper lobe, 3.6 mg. per gram. There was perhaps a slight dilution of the silica, owing to the tuberculosis.

The specimen removed in this case is the first of a series of tumor-like masses, first described by Lanza and Childs.[38] The condition is apparently a result of several factors operating together, as no one of the factors seems able to produce the result without the intervention of one or more other elements. Perhaps there are chronological, sequential and quantitative aspects of these factors. The conditions most commonly found to produce this result are chronic anthracosilicosis and progressive and parallel tuberculosis that does not advance too rapidly. The result appears to be a massive formation, many times simulating a tumor roentgenographically. If one judges from the progress in this case during seven years (the longest period for which we have been able to study the development of these masses), it must require a decade or more for their complete evolution. There seems to be slow extension around the borders of an atelectatic mass.

CASE 29.—A man, aged 39, a lead and zinc miner for fourteen years at Picher, Okla., presented symptoms of tuberculosis on his admission to the hospital. The lungs revealed bilateral obliterative pleuritis. There was no sign of the usual black pigment, the color being grayish red-brown. On the right side was a large fibroid cavity, crossed by vessels, which filled the whole upper lobe. Throughout the base were numerous silicotic nodules. The hilar nodes were a mass of fused fibrotic and calcified silicotic nodes that had embedded the vessels and esophagus. There were several diverticula in the esophagus. In the upper lobe of the left lung were several irregular cavities and a large number of silicotic tubercles with a small amount of coal pigment. In the lower lobe these nodules became smaller and fewer.

The microscopic picture in this case was that of tuberculosis of the usual type associated with silicosis. The silica content had an interesting distribution. There was 4.6 mg. per gram in the denser portions, with 3.3 mg. per gram in the less involved parts of the lung. The content of the hilar lymph nodes was 5.4 mg.;

38. Lanza, A. J., and Childs, S. B.: Bulletin 188, U. S. Pub. Health Serv., 1934, p. 418.

that of the bronchopulmonary nodes, 5.9 mg., and that of the paratracheal nodes, 3.4 mg., per gram, showing that the greatest amount of drainage had been toward the hilus and the overflow along the trachea (and perhaps through the diaphragm, as occurred in case 17). The more distant nodes contained only a little over half the quantity found in the hilus. A significant feature in this case was the lack of black pigment and the absence of the large masses so commonly observed when coal dust is a complicating factor. The lungs of the majority of miners in the Ozark region have a large amount of coal pigment.

CASE 30.—An American, aged 54, had an indefinite history of lead and zinc mining, but on clinical examination he was found to have mitral stenosis. The gross and microscopic examination of the pericardial, pleural and peritoneal cavities revealed tuberculous panserositis and definite silicotuberculosis, in which rather well developed silicosis was undergoing an early stage of tuberculous caseation (fig. 4 *c* and *d*).

CASE 31.—A man, aged 62, who had been a lead and zinc miner for seventeen years but had not been in the mines for eight years, entered the hospital with typical pulmonary tuberculosis.

The whole upper portion of the right lung was black, fibrous and slightly contracted, with an area of excavation in an early stage in the center, measuring from 2 to 3 cm. The diameter of this black mass was about 12 cm. There was a large, black nodule in the apex of the lower lobe of the right lung, measuring from 3 to 4 cm. A large mass, measuring 5 by 7 cm., extended from the hilus along the left subapical bronchus. In the hilar lymph nodes were large calcified masses. There were numerous small fibrotic nodules throughout the bases of both lungs. These observations corresponded with the shadows seen during the seven years of illness. The microscopic observations were similar to those in case 27, except that there was more pigment and less tuberculosis in this case.

The important feature in this case is the length of time that we were able to study the development of the huge masses so frequently seen in miners of the Ozark region. On the basis of the results of this study, it may be assumed that the condition was in progress for about twenty years.

CASE 34.—A man, aged 55, who had worked as a lead and zinc miner for thirty-three years, had the usual symptoms of pulmonary tuberculosis.

The upper and middle lobes of the right lung were contracted to one-fifth their normal volume. The lower lobe was of about the usual size but was completely consolidated, owing to caseous pneumonia. There was not as much periarterial and peribronchial fibrosis in this area as in other locations (fig. 6 *a*). The lymph nodes at the hilus were densely compact and black but did not resist the knife as completely as those in some cases of silicosis. In the lower lobe of the left lung small black foci were scattered in the parenchyma, and a large mass in the hilus was partially solid and made up of areas of black pigment interspersed with yellow-gray. There were marked dilatation of the heart and fibrinous pericarditis.

Microscopic examination of a lymph node, which was completely packed with whorls of old silicotic nodules, showed in the interstices between the nodules masses of black pigment with autolysis of large areas of the hyalinized tissue, leaving open spaces filled with fine granular black pigment. The adjacent atelectatic lung tissue

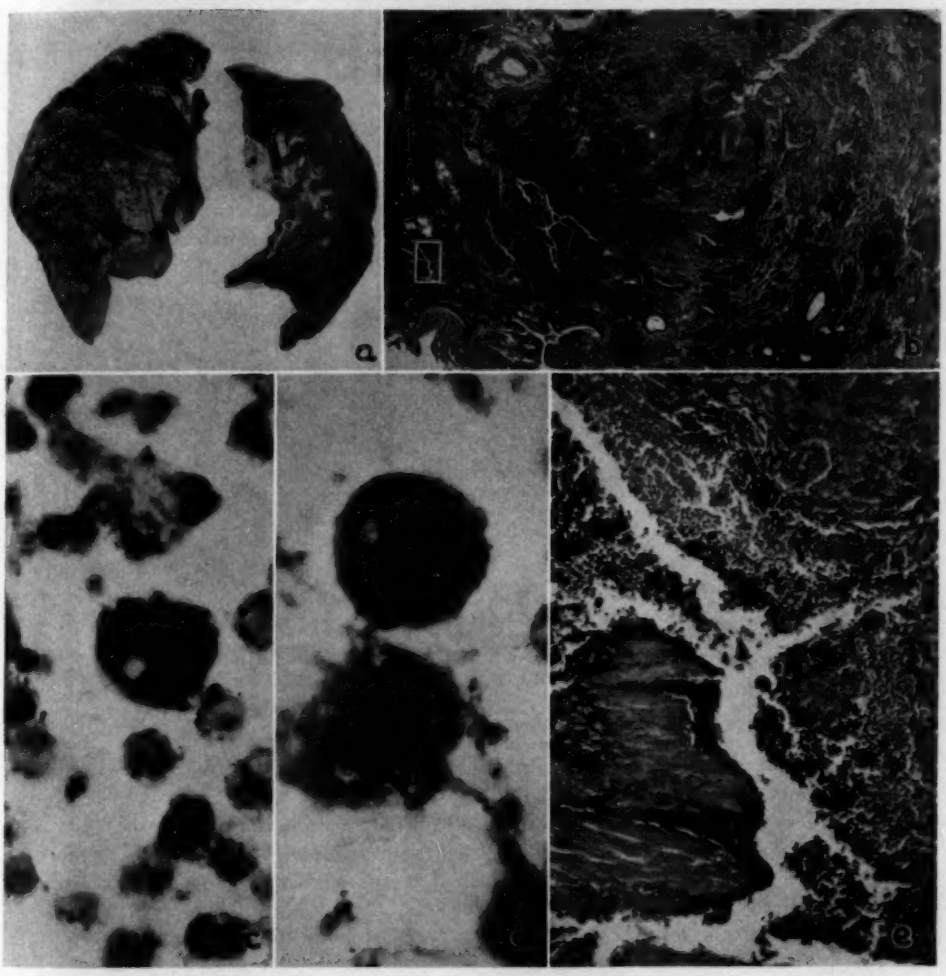

Fig. 6.—In *a* is shown a gross photograph of the anterior view of the lungs of a lead and zinc miner (case 34), revealing the accumulation of black pigment extending from the hilus in the left lung and the caseous pneumonia in the base of the right. Photomicrographs: *b*, of a section (× 3.5) of the black part of the lung shown in *a*, revealing whorls in the pigmented atelectatic tissue, with crevices due to autolysis; *c* and *d*, of phagocytic monocytes (× 900), showing the accumulation of pigment and the destruction of the cell, and *e*, of the area indicated in *b* (× 100), showing phagocytes in an autolyzed crevice. Hematoxylin-eosin stain.

revealed packed alveoli with fibrous and bulbous alveolar walls. Along the vessels the lymphatic structures were engorged with pigmented phagocytes and fibroblasts, some undergoing an early stage of whorl formation. Some alveoli were filled with polymorphonuclear leukocytes. The type of involvement observed may be described as a transition between that in case 27 and that in case 31.

A section from the black mass in the upper lobe of the right lung contained numerous old small silicotic whorls, measuring from 1 to 2 mm., scattered throughout the atelectatic lung tissue (fig. 6 *b*, *c*, *d* and *e*). Surrounding the whorls were usually masses of phagocytes containing black pigment. The cell seemed to enlarge and rupture, leaving the pigment free to be picked up again by other monocytic cells, appearing from the deep tissues. These phagocytic cells appeared identical with the cells arising from the alveoli to engulf the pigment.

The base of the right lung had the characteristic appearance of tuberculous pneumonia. The base of the left lung presented the usual picture of an early stage of lymphangitis and nodulation associated with silicosis, some of which showed early tuberculous involvement.

The silica content of the black mass was 11.3 mg. per gram, while that of the pneumonic tissue was only 1.7 mg. This illustrates the dilution of the silica by infiltrating leukocytes, or white blood elements, such as occur in pneumonia or caseous pneumonia.

Group *G*.—Patients with siderosilicotuberculosis.

Cases 36, 37 and 38.—The patients gave a history of having worked in iron mines for many years. We are unable to furnish further data. In the pooled samples of lungs there was an average amount of silica. Microscopic sections revealed whorls characteristic of silicotuberculosis throughout, with many tubercles undergoing caseation. The pigment was dark brown (iron) instead of the usual black seen in the lungs of coal miners. There was little difference between the appearance of these lungs and that of lungs in which coal dust complicates the picture.

Case 39.—An American salesman, aged 58, had worked in the lead and zinc mines for fifteen years but had been a salesman for the last twenty years and had suffered from pulmonary tuberculosis.

The upper lobe of the left lung was contracted to a mass one-fourth the usual size. It was black at the base and showed a few fibrous whorls, which became grayish toward the upper part as a result of caseation. There was a huge cavity, measuring about 3 cm. in diameter, in the apex. A few black foci were scattered throughout the lower lobe. The lung was pinkish gray around these areas. A cavity, surrounded with fibrous tissue, filled most of the upper lobe of the right lung. There were tuberculosilicotic nodules of varying sizes throughout the lower lobe and numerous black foci, such as are observed in lungs of other types. The hilar nodes were dense, black and fibrotic.

A feature of this patient's history is that when the sputum became black tubercle bacilli were also noted.

The finding of 5.1 and 4.1 mg. of silica per gram is not unusual.

It is noteworthy that the patient lived for seventeen years after a definite diagnosis of silicotuberculosis was made. During most of this time he worked and enjoyed good health.

CASE 40.—A barber, aged about 45, a coal miner for eleven years and a lead and zinc miner for eight, had a condition diagnosed as silicosis modified by tuberculosis.

The surface of the lungs was black, with a heavy fibrous cap over the upper lobe of the right lung. Over the base of the right lung and the surface of the diaphragm there was less pigment. The upper and middle lobes of the right lung were contracted to one-fourth the normal size. In the upper lobe was a large cavity, which communicated with a rather large cavity in the lower lobe. In the middle lobe was a solid mass of black tissue, presenting great resistance to the knife. The upper part of the lower lobe was similar to the middle lobe. Throughout this upper portion and the whole lower lobe were foci of gray-yellow nodules surrounded with black pigment. In some areas this black tissue could be seen to have the appearance of fibrous whorls. Some of the bronchi toward the base were filled with recent caseous masses (fig. 7 *a* and *b*).

The lower lobe of the left lung was similar to that of the right, and the upper lobe of the left lung, to the middle lobe of the right. The upper lobe contained a sharply circumscribed mass offering great resistance on cutting, in the center of which were numerous irregular gray caseous areas and irregular areas of softening. The contiguous portion of the lower lobe was also black and solid. All the lymph nodes were black and solid and cut with great resistance. They grated on the edge of the knife.

Microscopically, the hilar lymph node examined was made up of old silicotic whorls, which were densely packed and were undergoing an early stage of caseation and calcification. Between old hyalinized whorls were large accumulations of black pigment, most of which was lying free in small lakes of autolyzed tissue or between the heavy fibers. There were a few early foci of caseation, some of which were undergoing calcification.

In a focus of tuberculosis in one of the large tuberculosilicotic masses were all the transitional elements already described, from the heavy bands of hyalinized connective tissue, with much black pigment in and around them, to the pink-staining caseous tuberculous tissue (fig. 7 *c* and *e*).

A cluster of moderate-sized silicotic nodules, which, like the surrounding parenchyma of the lung, were becoming tuberculous, showed engorgement of all the lymphatics with black pigment cells and a marked emphysematous condition of the alveoli (fig. 7 *d*).

In this patient tuberculosis developed after he had mined coal for eleven years and quartz for eight years. Exposure to coal dust did not appear to shorten the course of the disease. If anything, it prepared the lung for the development of silicosis, which was more rapid than usual after exposure to silica. The oldest silicotic process developed in the hilar lymph nodes before the onset of tuberculosis. A transition in the type of lesion was reflected in the changing character of the tubercosilicotic nodules from the hilus outward. When the tuberculosis, however, reached a certain stage it transformed the old nodules into lesions of a definite tuberculous nature, finally ending in a typical tuberculous process.

It is of interest to note that coal miners have black sputum for from five to ten years after they have left the mines and that even later they may "spit black" if infection of the lung develops.

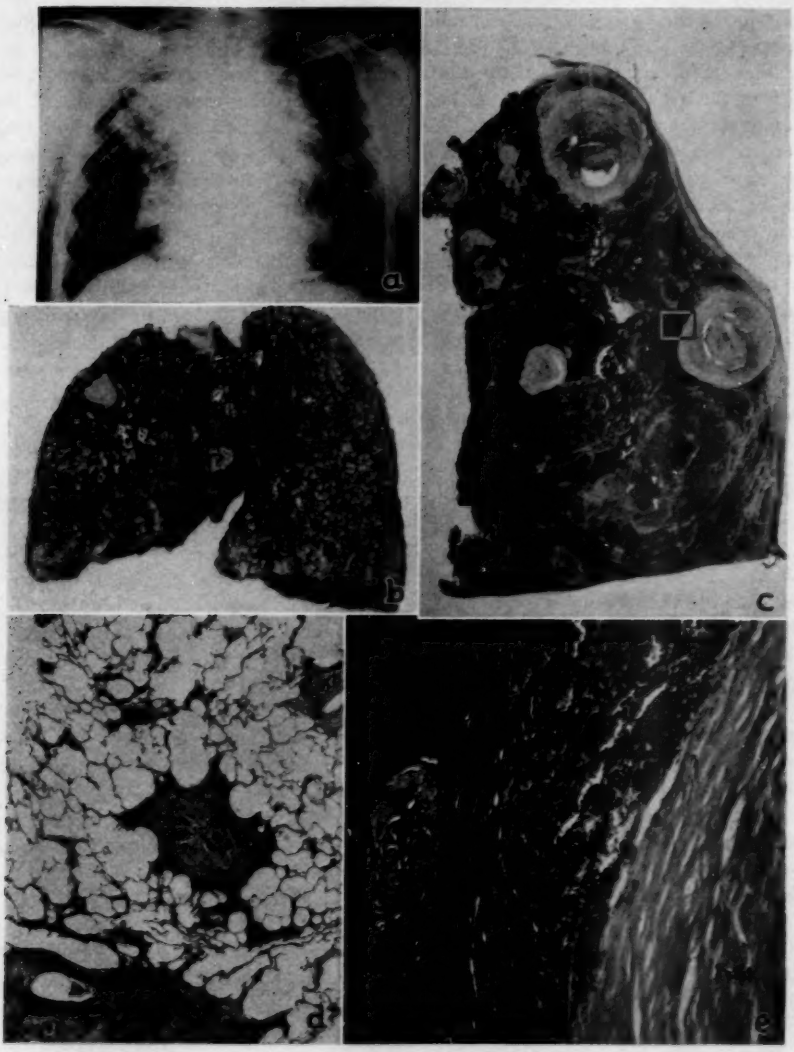

Fig. 7.—In *a* is shown a roentgenogram of the lungs of a man who had worked in coal and lead and zinc mines (case 40), revealing the tumor-like masses; in *b*, a gross photograph of the lungs of the man the roentgenogram of whose chest is shown in *a*, revealing the tumor-like masses undergoing ulceration and tuberculous caseation; in *c*, a low power photomicrograph (× 4) of tissue taken from the upper part of the larger black mass shown in *b*; in *d*, a low power photomicrograph (× 12) of a section taken from the lower lobe of the lung shown in *b*, and in *e*, a higher magnification (× 140) of the field indicated in *c*, showing silicotic whorls and masses of black pigment between the strands of fibrous tissue. Hematoxylin-eosin stain.

COMMENT

The chemical problems involved in this work will be considered first, as well as any new data that may be revealed by chemical analysis. The silica content of normal tissue has already been discussed, but the residue not volatilized in hydrofluoric acid needs further comment.

On the basis of the relationship of the residue to the silica content, the cases studied seem to fall into definite groups. Persons who work in the lead and zinc mines, in which the silica content of the rock is from 93 to 98 per cent, show a silica content from 1.8 to 15 mg. per gram (from 0.18 to 1.5 per cent) and a negligible nonvolatile hydrofluoric acid residue. Most coal miners have done a certain amount of work in rock, including the so-called "rock dusting." The typical lung of a coal miner (case 8) reveals a residue of 0.87 per cent, one half of which is silica and one half, nonvolatile substances. In certain patients a combined picture of involvement due to silica and coal dust has been shown (case 40), and the history confirms this.

Finally, there are the granite workers, stonecutters, rock miners and sand blasters and the great group of workers in rock containing silica in which the percentage of silicon dioxide is about 75 per cent or less and there is also much nonvolatile residue. Observations on this group are well represented by cases 22 and 23.

The source of the black pigment is another problem of great interest, although obscure at present. It was claimed by Jousset [39] that much of the pigment is due to the formation of sesquioxide of iron in pathologic tissues. It is clear that the pigment in the present series of patients must arise from one of four sources: (1) from the iron of the blood, as stated by Jousset, (2) from coal dust, (3) from carbon in the chert or (4) from carbon in ordinary air. Several of the patients in this series had coal mining experience, and the lungs were correspondingly intensely black. These patients had a definite chemical ratio indicating such an exposure. Likewise, persons who had been exposed to both chert and coal had a definite ratio showing a mixed process. On the other hand, in some lungs there were intense black masses but no chemical indication of any exposure to coal. In a few patients with similar histories brown and gray lungs were observed, with little or no black pigment. In instances of the last-mentioned condition there was usually a shorter time since the first exposure, suggesting either a gradual accumulation with time or a lack of pigment, as in case of exposure to gray chert.

After elimination of coal and iron on the basis of chemical analysis, only the chert and air are left as sources of the pigment, the greater amount of which comes from the chert.

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39. Jousset, A.: Presse méd. **36**:465, 1928.

Regarding the cytologic changes we have made observations that seem to supplement those already described and accepted.

After the phagocytes in the lymphatics become disintegrated, there is stimulation of fibrous tissue around the débris. Whether or not this tissue originates from "endothelial" cells is problematic. The cells seem to engulf the loose pigment once more and become elongated, and they resemble ordinary fibroblasts containing pigment. This process is shown in figure 1. Although this pigment is not synonymous with silica, it may be viewed as an indicator of the presence of silica. Finally, the cells are arranged side by side and take on the appearance of linear striations of fibroblasts, containing some pigment and enmeshing other pigment granules between them. There seems to be an attempt to wall off the toxic substance. As the process progresses, the fibroblasts take on more collagen, and the fibers become broader. Many bands of fibrous tissue are ultimately formed around the pigment in circular fashion, until the result is a whorl of hyalinized connective tissue. Although the silicotic whorl is nonspecific, as pointed out by Steuart,[17] the formation of the typical fibrotic whorls as an effect of any other substance than silica is unusual.

The complex of silicosis and tuberculosis is no doubt responsible for all but a small minority of the deaths from inhalation of silica dust. The resulting changes are different from those usually described and depend to a large extent on the time of infection with the tubercle bacillus and the size of the dose, in addition to the amount of silicosis. In the greater number of patients there seems to be occult or latent tuberculosis on which silicosis gradually develops, with a tuberculous process progressing slowly hand in hand with the silicosis and finally overtaking and overshadowing the silicosis and killing the patient.

In these instances there is a definite type of morbid anatomic picture, which may be called a silicotuberculosis complex. The microscopic changes represent every intervening stage from a typical silicotic whorl to a true caseous tubercle. As the tuberculosis gradually gains momentum the nodules become more tuberculous. As tuberculous caseation encroaches on the old silicotic nodule it "washes out" the heavy fibrils until they become homogeneous. Caseation may appear at intervals throughout the center. The heavy fibrous bands become thinner, and the process spreads outward, leaving in the central part islands of old silicotic nodules surrounded by more recent tuberculous caseation, which is encapsulated by tissue of the thinner type occurring in cases of "secondary" tuberculosis. Around the borders there is a characteristic tuberculous capsule, with here and there accumulations of newly formed lymphoid tissue. Some of these masses may involve the major part of the lobe. Usually, they slough into cavities before this occurs.

Interesting changes are also occurring in the old silicotic nodule at the hilus. Gradual caseation takes place, and there develops a peculiar shell-like calcification, which is more prone to form around the outside of the nodes than in the center, giving the appearance of an "exoskeleton" to the lymph nodes as seen in the roentgenogram (fig. 2*a*). The clinical and roentgenographic findings in this type are modified in proportion to the morbid anatomic changes. As the process becomes more tuberculous the physical findings become more characteristic of tuberculosis, and a transition to typical tuberculosis may occur. The roentgenogram reveals a more irregular type of "nodulation," some nodules becoming very large and more dense than the usual silicotic nodule. The process tends to progress toward the upper part and the apex of the lung as the tuberculosis gains the upper hand. In fact, a large number of the specimens of this type have little resemblance to lungs with silicosis. Simultaneous involvement with silicosis and tuberculosis may also be an explanation of some of the "acute" forms of silicosis. Perhaps the most vital question in the whole problem of silicosis is the extent to which silica predisposes to tuberculosis. In the light of the work of Gardner [40] and Kettle,[41] silica undoubtedly aggravates tuberculosis in experimental animals. The two diseases in human beings, however, may be fairly well evaluated if thoroughly studied post mortem.

As tuberculosis works havoc with the patient with silicosis, the presence of coal, iron, iron oxide, etc., appears to dampen the progress, at least temporarily, not only of silicosis but of tuberculosis. Even though the silica content may be far above the normal, the whorls of fibrous tissue are of much less extensive development. This effect may be due to several factors: There is so much dust (carbon) that it may dilute the silica, it may cause the removal of silica in the phagocytes, it may block the lymph flow and prevent absorption and it may dehydrate, owing to its tremendous surface, or absorb hydrated silica to its surface. It seems as though the silica is side-tracked temporarily. This action is borne out in the reports on coal miners, in whom Sampson,[41a] Cummins [42] and others did not find silicosis so prone to develop as in other miners. Cummins called the condition "anthracotic silicosis." When coal dust is present, there is also a variation of phagocytic activity. Coal seems to activate phagocytosis, and the cell soon becomes engorged and disintegrates instead of "freezing" into plaques, as in silicosis (fig. 7). Furthermore, coal dust seems to assist in the elimination of

40. Gardner, L. U.: Am. Rev. Tuberc. **20**:833, 1929.

41. Kettle, E. H.: Brit. J. Exper. Path. **3**:241, 1922.

41a. Sampson, H. L., in Kuechle, B. E.: Silicosis Symposium, Saranac Lake, New York, Employers Mutual Liability Insurance Co., 1934.

42. Cummins, S. L.: Lancet **1**:235, 1931.

silica when the two are inhaled together, as Carleton [43] suggested. When, however, exposure to silica occurs after the lymphatics are plugged with coal dust, as in case 40, this cleaning action cannot take place, and the effect is more serious than in normal persons. This is what appears to have occurred in the cases at Picher, Okla., reported by the United States Bureau of Mines,[44] in which previous coal mining did not appear to afford protection against silicosis. After the silica mining began, the time of survival was actually shorter than for the normal man, yet the addition of the period of coal mining made the time much longer. All that the coal mining did, therefore, was to slow down the progress of fibrosis while the man was working in coal, allow the accumulation of silica in the tissues and permit more rapid development of silicosis as a result of the more concentrated silica acting on a lung with impaired function.

For reasons similar to those in the case of silica, tuberculosis is said to be delayed by coal pigment, as affirmed by Cummins,[42] Collis [1] and Leclercq and his co-workers.[45] Cummins gave several reasons, which are based largely on the adsorptive properties of coal dust on the tubercle bacillus and tuberculin.

If one concedes, then, that both silicosis and tuberculosis are retarded in coal miners, one is not to assume that the coal miner is free from danger. This has been emphasized by Harrington and Davenport [5] and is borne out in cases of coal miners who become silica miners.

Most important of all, however, coal and iron seem to pave the way for acute infections. Just as tuberculosis causes the greater damage in cases of silicosis, the acute diseases are the bane of coal miners, iron miners, molders and persons in similar types of work in which silica plays a lesser rôle in the process. But an instance of pure dust disease rarely occurs, except in experiments. Usually more than one dust is present, and infection nearly always is present or occurs later. Whether tuberculosis or acute infection is predominant seems to depend on whether the silicotic fibrosis or the blocking of the lymphatics is more marked.

In the lead and zinc mines there is much less pigment than in the coal mines, but there is enough in the presence of pure silica to form large tumor-like masses of granulation tissue. As the process advances, whether owing to tuberculous infection or to the autolysis of broken cells, open spaces are formed between the fibrils of fibrous tissue, which gradually enlarge into cavities. These cavities are not like the usual

43. Carleton, H. M.: J. Hyg. **22**:428, 1924.

44. Meriwether, F. V.; Sawyers, R. R., and Lanza, A. J.: Technical Paper 552, U. S. Dept. Interior, Bureau of Mines, 1933.

45. Leclercq, J.; Bréhon, P., and Muller, M.: Bull. Acad. de méd., Paris **108**: 1088, 1932.

tuberculous cavities; they are more like a confluence of fissures and crevices at first, leaving large bulbous projections extending into the center.

While we have described perhaps the most common associated conditions, there are many other factors that modify both the silicosis and the tuberculosis. It has been reported that limestone, gypsum and other such soluble forms of minerals favor both conditions. On the other hand, future studies may reveal that some of these substances are detrimental and dangerous. Especially is this true of kaolin and similar substances, if one is to judge by the work of Gye and Kettle.[15]

There is no uniformity of opinion about the time of appearance of silicosis or modified silicosis. It seems to vary largely with the source of the silica and the particular work. In the cases at Picher the three stages appeared at the end of 11, 14 and 17 years, respectively, and this is a fair average, according to the reports in the literature. In some occupations and persons, however, disease develops in a very short time. Pancoast and Pendergrass [38] reported a case of very acute silicosis appearing one year after the patient had worked in a sand-pulverizing plant for thirty-five days. In other cases the average period of exposure was two and one-half years. Lochtkemper and Telegy [7] reported that silicosis developed after two years spent in a polishing-powder factory and in sand-blasting when a full blast of air was used. Particularly did the authors stress the danger of cement work, in which powdered sand is mixed with clay. In one patient working in a crushing mill, the disease developed after three months. Britton and Head [46] reported that in one patient silicosis developed twenty-three years after an exposure of four months. Chapman [47] reported cases of the development of acute silicosis in eight, twenty-one and twenty-nine months on exposure to cement dust of high silica content. The average minimal period of exposure required for causing silicosis, however, is placed at two and one-half years. The shortest time of exposure in this series was six months in a cement factory, in the case of a man in whom silicotuberculosis developed ten years later.

Likewise, there is no definite opinion in regard to the quantity and quality of particles necessary to cause silicosis. In general, it is accepted that more than 5,000,000 particles per cubic foot of air, containing 6 per cent or more of silica and less than 10 microns in size, are dangerous. In the light of the results of preceding study there may be much variation from this standard.

Little has been said concerning extrapulmonary complications in cases of silicosis. Perhaps the most important are cardiac changes, due

46. Britton, J. A., and Head, J. R.: J. A. M. A. **96**:1938, 1931.
47. Chapman, E. M.: J. A. M. A. **98**:1439, 1932.

to the burden thrown on the right side of the heart as a result of the gradual compression and obliteration of the pulmonary vessels by the fibrous tissues surrounding these vessels. In nearly all the cases the heart weighed from 350 to 500 Gm. and had a thick right ventricular wall. The hearts of a few persons with less advanced disease revealed nothing abnormal, indicating that cardiac changes appear only in the advanced stages. The myocardial changes are usually those characteristic of hypertrophy except in older men, in whom definite damage to the muscle appears.

Not only is there peripheral calcification of the lymph nodes but this becomes so markedly increased that sometimes it causes the organs of the mediastinum to fit between the nodes as though in a cast. This leads to adhesions, diverticula and sometimes perforations of the esophagus and buckling of the great vessels.

Only brief mention need be made regarding the collateral diseases that do not enter into the actual process. Syphilis, for example, seems to exert a serious systemic effect, which aggravates pneumonoconiosis. This was noticeable in the four patients in this series who had positive Wassermann reactions. The patient having cancer of the lung presented no silicosis but an advanced stage of pneumonoconiosis with emphysema.

Finally, there are many other organs that are or may be affected to a greater or less degree, but their involvement has no immediate bearing on the problem of pneumonoconiosis, and consideration of this subject has been omitted.

In conclusion, it seems that there are many dusts that may, under certain circumstances, cause damage in a rather short time, that a host of combinations of dusts and diseases are not yet understood, that there are many extrapulmonary and collateral changes and that many other observations lack explanation. It is obvious, therefore, that the study of pneumonoconiosis awaits further development.

SUMMARY

A report is made of the results of the chemical and pathologic examinations of forty patients with pneumonoconiosis and of those of twenty control patients. The silica content of normal lung tissue was found to correspond fairly well to values recently reported in the literature. Some specimens were low in the amount of silica, in some instances probably owing to dilution by the action of inflammatory tissue, as in cases of pneumonia. In patients who have worked in silica and show a content of 2 mg. or more per gram of dried lung tissue (0.2 per cent), silicotic nodulation is usually present, but the degree need not necessarily be in proportion to the quantity of silica. The quantity of the silica does not appear to bear any relation to the time of exposure. The content of

silica in the lymph nodes in early life was found to be about the same as that in lung tissue, but it increases gradually with age until in most adults living in cities the content is about 6 mg. per gram of dried tissue (0.6 per cent). In cases of exposure to silica, the content of the lung gradually increases, usually to exceed the content of the lymph node, and reaches in extreme instances nearly 25 mg. per gram of dried tissue (2.5 per cent). In workers in pure quartz there is little or no hydrofluoric acid residue after the silica is volatilized, while this residue in granite workers, stonecutters, coal miners, molders and representatives of certain other occupations has a definite ratio to the amount of dust inhaled.

In the advanced stage of silicosis there is a gradual constriction of the pulmonary vessels with resulting hypertrophy and dilatation of the right side of the heart. There is also fixation of the lymphatics around the hilus, which leads to fixation of the bronchi and occasionally to diverticulosis and perforation of the esophagus.

Tuberculosis seems to be present in all but a minority of patients with silicosis and to progress slowly with little remission, sometimes producing large masses in the lungs and lymph nodes which undergo slow caseation. Tuberculosis seems to change the silicosis from a benign to a slowly progressive confluent disease, with usually an acute and sudden termination. The severity of the process depends on the time of the entrance of the tubercle bacillus and on the quantity of the bacilli present, as well as on hereditary factors in the host. The lymph nodes of patients with this condition gradually undergo calcification, the distribution of which is rather diffuse but more marked just beneath the capsule of the lymph node and which has been well described as "egg-shell" calcification. The silicotic nodule in such patients usually undergoes gradual transformation from a typical fibrous silicotic whorl to a nodule that becomes more and more like, and ultimately indistinguishable from, a nodular tubercle.

The silica content of the lungs of coal miners may become twice that at which silicotic nodules usually appear, without specific nodulation being shown. The nonvolatile hydrofluoric acid residue for coal miners is only slightly less than the soluble silica content. Silicosis, tuberculosis and silicotuberculosis are retarded by exposure to coal dust, sometimes resulting in the development of large black masses, larger and more benign than those of the tuberculosilicotic complex. Uncomplicated anthracosis is generally free from nodular fibrosis but is, nevertheless, of grave significance on account of a predisposition of the subject to pneumonia and acute inflammation. When a coal miner works in silica, the lymphatics seem to be blocked and show no increase in silica content, while the content of the parenchyma rises to high levels, perhaps more rapidly than in miners with normal lungs.

HISTIOCYTIC RESPONSE IN OMENTAL CARCINOMATOSIS

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It is a well known fact and a common microscopic observation that leukocytic infiltration in and around tumors is of frequent occurrence. The infiltrate may consist of lymphocytes, which are encountered most frequently, neutrophilic polymorphonuclears, eosinophils, mononuclear leukocytes, plasma cells and sometimes phagocytic histiocytes and foreign body giant cells. Because phagocytic histiocytes are least conspicuous in tumors and when found are usually associated with primary and metastatic neoplasms of the central nervous system, their abundant presence in an omentum which has been invaded by tumor not originating in the central nervous system warrants a report.

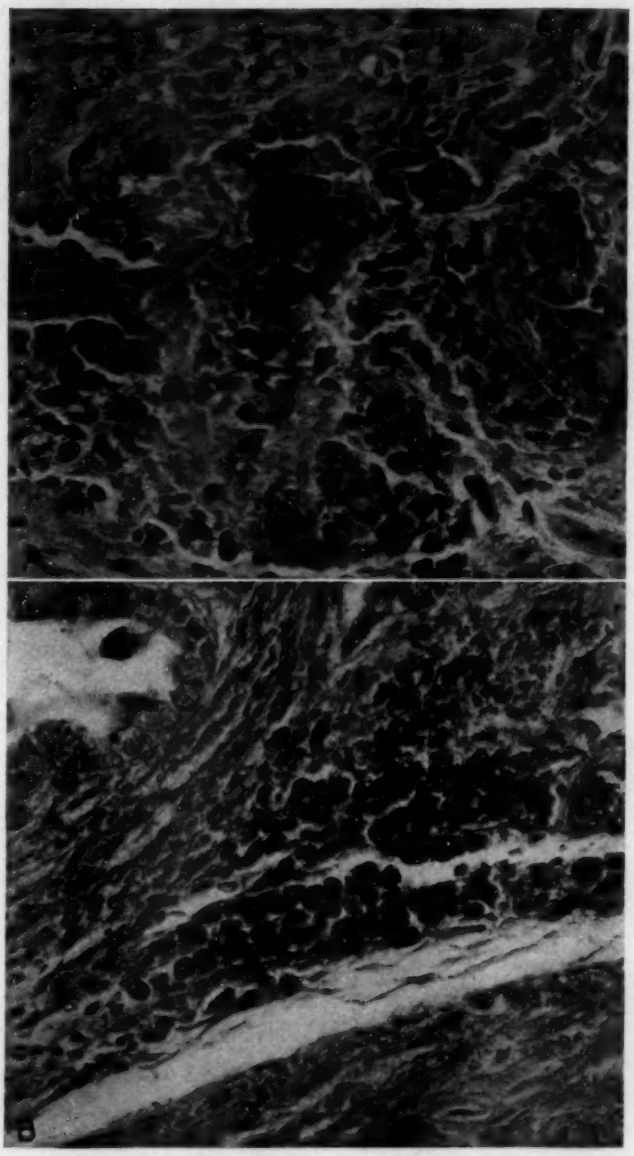
In a histologic review of seventy-five autopsies in which omental carcinomatosis was found, there has been observed in 35 per cent of the cases an almost total absence of the usual leukocytic infiltrate but an extremely great abundance of pigmented macrophages. These cells were flat and angular, their nuclei eccentrically located and kidney-shaped. Their cytoplasm presented large quantities of pigment (*A* in figure).

In the same sections there were seen numerous transitional forms of these cells. We were able to observe transitions from lymphocytes and mononuclear leukocytes to large macrophages. In some instances, so-called exudate polyblasts were observed. These were large spherical cells with two or more nuclei each, the cytoplasm having many inclusions and sending out pseudopodia.

The relation of these macrophages to the tumor tissue was of interest. The usual infiltration of lymphocytes in and around the tumor cells was absent. These pigmented macrophages were arranged in groups and were present only in areas which were free from tumor cells (*B* in figure).

In no instance was there observed any phagocytosis of the living tumor cells by the macrophages.

From the Pathology Laboratory, New York City Cancer Institute.



A, islands of pigmented macrophages. *B*, tumor cells and pigmented macrophages.

COMMENT

In a recent review by Taylor and Wilson [1] instances are cited in which retrogression of omental carcinomatosis occurred. It is the belief of these two investigators as well as of others, particularly Konjetzny,[2] that in the cancerous omentum there are reactive blood changes taking place characterized by the presence of histiocytes and macrophages, and that this denotes a healing process. In none of our cases have we observed retrogression of a metastatic omental tumor, and in many instances the autopsy occurred three or four years after the initial diagnosis.

It is our belief that the histiocytic response is a defense reaction against a local injury produced by the tumor cells in the omentum, the function of the responding cells being the active phagocytosis of débris, such as dead tumor cells and bacteria, and that in no way do they take an active part in the local destruction of the living tumor cells. This view has been accepted by Dr. Chambers and Dr. Grant [3] of the department of cellular physiology of New York University. They have observed in tissue culture that living tumor cells are negatively chemotactic, while the dead cells exhibit evidences of positive chemotaxis.

1. Taylor, H. C., and Wilson, E. A.: Am. J. Cancer **16**:1305, 1932.
2. Konjetzny, G. E.: München. med. Wchnschr. **65**:292, 1918.
3. Chambers, R., and Grant, C. G.: Personal communication to the authors.

MESENTERIC VASCULAR OCCLUSION OF ARTERIAL AND OF VENOUS ORIGIN

REPORT OF NINE CASES

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Several workers have shown experimentally that obstruction of the portal or mesenteric blood vessels is accompanied by an effusion of blood and bloody fluid into the peritoneal cavity, into the tissues supplied by the vessels in question and into the lumen of the involved gut. This effusion has been found large enough in many instances to account for the death of the animals on the basis of secondary surgical shock. "Secondary shock" is used here to indicate the syndrome due to loss of large amounts of plasma-like fluid or blood from the circulating blood stream. In the literature only one report [1] was found of clinical observations concerning loss of blood or circulating fluid and resultant secondary shock in such vascular obstructions. Clinically these occlusions may be divided into four types: (1) thrombosis of the portal vein, due either to pylethrombophlebitis or to ordinary thrombosis; (2) occlusion of the mesenteric vein, usually due to thrombosis and often associated with thrombosis of the portal vein; (3) occlusion of the mesenteric artery, often embolic in origin, and (4) intestinal strangulation, in which often both veins and arteries are occluded. In the present article the literature concerning these four types is reviewed briefly, and nine cases of mesenteric vascular occlusion observed at the University of Chicago Clinics during the past eight years are presented. These cases are discussed especially from the standpoint of the loss of fluid and secondary surgical shock.

REVIEW OF THE LITERATURE

Occlusion of the Portal Vein.—In 1856 Oré [2] showed that in dogs ligation of the portal vein produced rapid death, usually in less than an hour. On the other hand, partial ligation of the vein enabled the dogs to live after complete ligation at a later stage. In these animals secretion of bile continued despite the complete ligation of the portal vein.

From the Departments of Surgery and Pathology of the University of Chicago.

1. Boyce, F. F., and McFetridge, E. M.: Internat. S. Digest **20**:67-80, 1935.

2. Oré: (*a*) Compt. rend. Acad. d. sc. **42**:497, 1856; (*b*) **43**:463, 1856; (*c*) J. de l'anat. et physiol. **1**:556-565, 1864.

At about the same time Gintrac [3] collected thirty-four instances of obstruction of the portal vein, six of which were observed in his own clinic. Gintrac noted that the secretion of bile in the patients continued. One patient had considerable ascites at necropsy.

In 1859 Claude Bernard [4] studied the problem experimentally but was unable to offer an explanation of the resultant death. He stated: "When one ligates the portal vein, death is produced either immediately or at least very rapidly. The operation is soon followed by weakness, collapse and death supervenes after several hours. The intestines become black, engorged with blood; the lumen is the seat of hemorrhage and a bloody diarrhea occurs." Bernard believed that such rapid death must be from other causes than the bloody engorgement of the intestines. Eighteen years later he altered his views.[5] He then adopted the idea that the local accumulation of blood is the cause of death. Bernard did not mention the experiments of von Tappeiner [6] performed in 1873 with results in opposition to the exsanguination theory.

In 1875 Solowieff [7] showed that in dogs ligation of the branches of the portal vein—for example, the superior mesenteric and splenic branches—could be done at separate operations without resultant death. If these vessels were tied at once, death uniformly resulted in from four to twenty-two hours. This interval before death is somewhat longer than any found by other authors. Ehrhardt [8] also found that ligation of the branches of the portal vein could be performed in separate stages without fatality and with only minor effects on the liver.

Erlanger and Gasser [9] produced obstruction of the portal vein by injecting epinephrine hydrochloride and the spores of Lycopodium into the vein. Janeway and Jackson [10] produced portal obstruction by high ligation of the vena cava.

De Jong [11] reported nine cases of obstruction of the portal vein. He classified such obstructions as being: (1) radicular, in the mesenteric branches; (2) truncal, in the main vein, and (3) terminal, in the intrahepatic branches. In his series there was one case of the terminal or

3. Cited by Oré.[2e]

4. Bernard, Claude: Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme, Paris, J.-B. Ballière & fils, 1859, vol. 2, pp. 190-196.

5. Bernard, Claude: Leçons sur le diabète et la glycogenèse animals, Paris, J.-B. Ballière & fils, 1877, pp. 316-319.

6. von Tappeiner, H.: Arb. a. d. physiol. Anstalt zu Leipzig **7**:11-64, 1872.

7. Solowieff, A.: Virchows Arch. f. path. Anat. **62**:195-200, 1875.

8. Ehrhardt, O.: Arch. f. klin. Chir. **68**:460-467, 1902.

9. Erlanger, J., and Gasser, H. S.: Am. J. Physiol. **49**:345-376, 1919.

10. Cited by Erlanger and Gasser.[9]

11. de Jong, R. de Josselin: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:160-194, 1912.

intrahepatic type. Another case is of interest in that there were fresh antemortem clots in the mesenteric branches and an old, partially organized clot in the main trunk. All but one of the patients had extensive peritoneal exudate, 60 liters being obtained in one week from one of them. Sprengel [12] reported a case of old clot in the portal vein with fresh antemortem clots in the radicles of the mesenteric veins. Simonds [13] described a case of chronic occlusion of the portal vein with partial canalization and calcification. Collateral circulation was established between the splenic and left renal veins. When splenectomy was performed in an attempt to ameliorate the intestinal hemorrhages, this collateral circulation was destroyed and death resulted. Simonds collected reports of ninety-four cases of chronic occlusion of the portal vein from the literature; only six of these reports are in English.

Neuhof [14] in 1913 carried out experiments on ligation of the portal vein in dogs. He found that death occurred uniformly in from fifty to ninety minutes after ligation, that at necropsy there was bloody fluid in the peritoneal cavity, that the mesentery and the bowel were edematous and hemorrhagic, that the spleen was markedly enlarged and that there was some blood in the intestinal lumen. He stated, "It is now generally held that death in such instances is due to shock." He then goes on to show that life is compatible with complete occlusion of the portal vein if the occlusion is gradually induced, and that this tolerance is due to the development of a collateral circulation. Dragstedt [15] showed that the portal vein of the dog could be ligated by a two stage operation.

Elman and Cole [16] reported that in a series of nineteen dogs the average period of survival after ligation of the portal vein was sixty-six minutes. Lymph and blood collected from the region of the portal vein after ligation of the vein were injected into guinea-pigs and white mice without producing signs of toxicity. The entire intestinal tract was then removed from each dog, weighed and the weight compared with that of the normal intestinal tract as determined in a control series. The average increase in weight amounted to 5.2 per cent of the body weight.[17] A series of cats averaged 3.4 per cent increase in weight. In a series of control cats the authors found that death followed a 2.7 per cent loss of blood by hemorrhage from the femoral artery. In some but not all of the animals with experimental obstruction of the

12. Sprengel: Arch. f. klin. Chir. **67**:587-619, 1902.

13. Simonds, J. P.: Chronic Obstruction of the Portal Vein, Arch. Surg. **33**:397-424, 1936.

14. Neuhof, H.: Surg., Gynec. & Obst. **16**:481-488, 1913.

15. Dragstedt, L. R.: Science **73**:315, 1931.

16. Elman, Robert, and Cole, W. H.: Arch. Surg. **28**:1166-1175, 1934.

17. Elman, Robert, and Cole, W. H.: Proc. Soc. Exper. Biol. & Med. **29**: 1122-1123, 1932.

portal vein there was transudation of bloody fluid into the lumen of the bowel. There was very little peritoneal exudate.

Boyce, Lampert and McFetridge [18] performed experiments with results which they interpreted to be somewhat at variance with those of Elman and Cole.[17] In seven dogs they found the increase in weight of the viscera after death from ligation of the portal vein to average 3.05 per cent of the body weight. In another series dogs were bled an average of 4.56 per cent of the body weight without shock or death resulting. They concluded therefore that in experimental ligation of the portal vein the loss of blood is insufficient to account for death. They corroborated the work of other writers in reporting that gradual ligation of the portal vein is compatible with life and that intravenous infusions prolong life. It is to be remembered in considering these results as opposing the theory that loss of blood causes death from portal ligation that the 3.05 per cent loss of fluid probably does not represent pure blood but more plasma than cells. It is well known that the loss of a certain amount of whole blood is less serious than the loss of a similar amount of plasma, and under certain conditions Johnson and Blalock [19] found that dogs would die after an average loss of 2.6 per cent of the body weight in blood plasma by plasmapheresis. Boyce, Lampert and McFetridge [18] concluded, however, that loss of blood is an important factor. They reported that a neurogenic factor, as in primary shock, is the initiating mechanism and that the loss of blood only accentuates and perpetuates the low blood pressure due to the primary shock. These authors also reported a decreased clotting time after ligation of the portal vein.

Thole [20] reported that section of the vagi postpones the inevitable death following ligation of the portal vein. Rost [21] concluded that death following ligation of the portal vein is due either to collapse of unknown origin or to intestinal congestion and infarction; that it is not due to elimination of the liver function is shown by results obtained with Eck fistulas demonstrating that life is compatible with short-circuiting of the liver.

Occlusion of the Mesenteric Vein.—Mayo-Robson [22] reported a case of penetrating wound of the abdomen in which the superior mesenteric vein was involved. Operative ligation of the vein with lavage of the

18. Boyce, F. F.; Lampert, R., and McFetridge, E.: J. Lab. & Clin. Med. **20**:935-943, 1935.

19. Johnson, G. S., and Blalock, A.: Arch. Surg. **22**:626-637, 1931.

20. Cited by Rost.[21]

21. Rost, F.: The Pathological Physiology of Surgical Diseases, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1923, pp. 117-119 and 233-237.

22. Mayo-Robson, A. W.: Brit. M. J. **2**:77-78, 1897.

abdomen and intravenous saline infusion resulted in recovery. In a later article, Wilms [23] challenged Mayo-Robson's report, saying that the superior mesenteric vein can be reached only above or behind the pancreas and that the injury probably involved some other vessel. He presented experiments on animals showing that obstruction of the superior vena cava causes infarction and reported a case of injury to the superior mesenteric vein. Delatour [24] believes that thrombosis of the mesenteric veins may cause death after splenectomy. He had a patient die twenty-four days after operation, and at necropsy the peritoneal cavity contained a pint or so of blood-stained serum. It is possible that some venous occlusion existed before operation in Delatour's case.

Elliot [25] in 1895 reported the first cure after operative resection of the infarcted bowel. When he opened the peritoneal cavity a large amount of bloody fluid escaped. The occlusion was venous. Elliot stated, "After a careful search I have been unable to find a single case of strangulation or twist where anything like this amount of blood was found either in the intestines or peritoneal cavity." Elliot cited Orth as authority for the statement that the most striking examples of hemorrhagic infarction are to be met with after venous stoppage.

Welch [26] stated that venous thrombosis sometimes ascends from ulcer of the intestine and sometimes descends from thrombosis of the portal or splenic vein. Sometimes portal thrombosis leads to mesenteric thrombosis owing to the long since developed collateral circulation. At other times portal thrombosis is rapidly terminated by extension of the thrombosis into the mesenteric veins. The portal thrombosis itself, Welch stated, was more often primary than secondary to cirrhosis. Welch noted marked hemorrhagic infarction of the bowel and mesentery and bloody fluid in the peritoneal cavity following thrombosis of the mesenteric vein.

Occlusion of the Mesenteric Vein or Artery.—So many reports in the literature discuss both types of obstruction that these papers must be mentioned under one heading. Elliot's [25] second case was one of occlusion of the mesenteric artery. He found reports of fifty cases of arterial occlusion in the literature. There was an embolus from the left side of the heart in nineteen of twenty-three cases sufficiently investigated. Marked abdominal distention and the escape of blood into the intestines and peritoneal cavity were the most natural results of the

23. Wilms: München. med. Wchnschr. **48**:1277-1279, 1901.

24. Delatour, H. B.: Ann. Surg. **21**:24-28, 1895.

25. Elliot, J. W.: Ann. Surg. **21**:9-23, 1895.

26. Welch, W. H.: Thrombosis and Embolism, in Allbutt, T. C.: System of Medicine, New York, The Macmillan Company, 1901, vol. 6, pp. 153-285.

infarction. Melena occurred in thirteen of twenty cases with sufficient data. There was diarrhea in nine of twenty cases. Elliot found reports of only fourteen cases of thrombosis of the mesenteric vein. This condition was even more rapidly fatal than arterial thrombosis. The local symptoms were about the same; diarrhea, however, was much less common. One patient recovered without operation, and only three were operated on, with fatal issue in all. He concluded, "One would expect more profuse bleeding from plugging of the vein than of the artery, because with the vein only occluded the artery would still continue pumping blood into the tissue."

Jackson, Porter and Quinby [27] reviewed two hundred and fourteen cases, including twenty-seven of their own, in a comprehensive study. One hundred and ninety-seven could be separated into instances of arterial or venous mesenteric occlusion; one hundred and twenty, or 61 per cent, were instances of arterial and seventy-seven, or 39 per cent, of venous occlusion. In 20 per cent of cases of both types the symptoms were of less than twenty-four hours' duration, and in about 50 per cent, of less than seventy-two hours' duration, inclusive. In seven cases of each group the symptoms were of more than two months' duration. The venous occlusion was more steadily progressive; the arterial took the form of attacks and remissions. There were fourteen recoveries, some of which were spontaneous. Sixty-four per cent of the patients were males and 36 per cent females. Seven of the patients were in the first two decades of life, twenty-eight in the second two, forty in the third two, twenty-three in the fourth two and five between 80 and 100 years of age; over half were between 30 and 60 years of age. Pain was absent in only 8 per cent and was generalized in 51 per cent. Obstipation was present in 22 per cent, melena in 41 per cent, tenderness in 70 per cent and distention in 78 per cent. Forty-seven patients were operated on and only four of these recovered (94 per cent mortality). Many of the patients had a large amount of peritoneal exudate at operation or necropsy. The authors concluded: "In the majority of cases there is free fluid in the general cavity, often blood stained, and usually in amounts sufficient to be demonstrable during life."

Reich [28] and Loop [29] reviewed the literature. The latter author reported nine operative cases with one recovery. He pointed out several significant signs and symptoms. There was a large amount of sticky peritoneal fluid in all cases, and the mesentery and the wall of the bowel were edematous. The bowel contained fluid and but little gas. There was slight, if any, muscle spasm, the flaccidity of the abdominal muscles

27. Jackson, J. M.; Porter, C. A., and Quinby, W. C.: J. A. M. A. **42**:1469-1475, 1904; **43**:25-29, 110-114 and 183-187, 1904.

28. Reich, A.: Ergebn. d. Chir. u. Orthop. **7**:515-597, 1913.

29. Loop, R. G.: J. A. M. A. **77**:369-373, 1921.

being a striking feature in a patient suffering severe pain. The abdomen was bloated rather than distended, and dulness was present. The condition was essentially afebrile, the temperature seldom going above 100 F. Loop did not differentiate between arterial and venous types of occlusion. Meyer [30] also made no distinction between arterial and venous types in his review of ninety-two cases.

Boyce and McFetridge [1] are practically the only authors who mentioned the factor of secondary surgical shock and the necessity for repeated determinations of the blood pressure in clinical cases of mesenteric vascular occlusion. They postulated: "The state of shock characteristic of this condition is rarely evident immediately. As the duration of the disease increases, however, and as more and more blood is lost into the mesentery, especially if the occlusion is venous, the blood volume decreases and the typical symptoms of shock appear, a subnormal temperature, a falling blood pressure, a fast thready pulse, clammy perspiration and marked pallor." They pointed out that mesenteric vascular occlusion is the most fatal of all abdominal emergencies. To show how increased interest in the condition may cause an apparent rise in its incidence, they cite Watson's statistics. Watson found records of six cases in nine years at the Boston City Hospital, and then, after he became interested in the condition, he observed eight cases himself in one year. Trotter [31] differentiated between arterial and venous types of obstruction. Donaldson and Stout,[32] after quoting McIver as stating that mesenteric thrombosis was the cause in 3 per cent of his series of three hundred and thirty-five cases of intestinal obstruction, went on to report three cases of venous thrombosis, all with peritoneal exudate.

Occlusion of the Mesenteric Artery.—Early reports of cases of arterial occlusion include those by Hodgson [33] on an obstruction of the celiac artery due to aneurysm, a specimen of such obstruction in the museum of Guy's Hospital and a personally observed occlusion of the superior mesenteric artery; one by Chaussier [33] in 1818 on an occlusion of the superior mesenteric artery and celiac artery; one by Fleischmann [33] in 1815 on an occlusion of the same vessels by aneurysm and one by Meli [33] in 1821 on an obstruction of both mesenteric arteries and veins. In the last-mentioned case the peritoneal cavity was filled with bloody fluid containing clots; there were ecchymoses in the intestine and mesentery as well as blood in the intestinal wall and lumen.

30. Meyer, J. L.: Ann. Surg. **94**:88-96, 1931.

31. Cited by Ackman, F. D.: Canad. M. A. J. **25**:657-663, 1931.

32. Donaldson, J. K., and Stout, B. F.: Am. J. Surg. **29**:208-217, 1935.

33. Cited by Tiedemann, F.: Von der Verengung und Schliessung der Pulsadern in Krankheiten, Leipzig, Karl Gross, 1843.

Chiene [34] reported a case of obliteration of both mesenteric arteries and the celiac artery with adequate collateral circulation. Virchow [35] in 1847 described a necropsy on a patient who had a clot in the superior mesenteric artery with some turbid fluid in the small pelvis. Beckmann [36] in 1858 described a woman aged 80 with embolism of the superior mesenteric artery but made no mention of peritoneal fluid. Gerhardt [37] collected eleven instances in 1863, including one of his own. Ponfick [38] reported three cases of embolism of the superior mesenteric artery and mentioned the finding of little peritoneal fluid in the second case and considerable in the third; he made no statement as to the first case in this respect. Litten [39] experimented with dogs and concluded that although the intestine is not supplied by anatomic end-arteries functionally the arteries are such, and that death always follows ligation of the main trunk of the superior mesenteric artery. In these experiments there was hemorrhagic peritonitis. Cohnheim [20] believed that the only way that hemorrhagic infarcts could result from ligation of the artery alone was by venous backflow. Cohn,[20] however, believed this explanation insufficient because hemorrhagic infarction was just as pronounced or even more so when the vein as well as the artery had been ligated. Cohn believed there was an inflow of arterial blood from the margins of the infarct. Sprengel [12] added a new aspect to the question by reporting a case of anemic infarct of the intestine from arterial occlusion. He presented four cases, in one of which there was an anemic infarct. In two of the cases he observed a large amount of peritoneal fluid and in a third an enormous amount; concerning the fourth in this respect, he presented no data. Niederstein,[20] working under Sprengel, believed anemic infarcts occurred when both arteries and veins were occluded, as by injections of paraffin. Marek [20] showed, however, that injections of paraffin blocked off the arterial anastomoses. He believed that if the arteries are completely occluded an anemic infarct occurs. This work of Marek's is one of the most important links in the chain of evidence indicating that inflow from the arteries at the edge of an infarct is the cause of the hyperemia in occlusion of the mesenteric artery.

The work of Mall and Welch [34] throws light on the mechanism by which hemorrhage is produced after arterial infarction of the intestines. They reported that after ligation of a mesenteric artery the segment of

34. Cited by Welch.[26]
35. Virchow, R.: Arch. f. path. Anat. **1**:272-378, 1847.
36. Beckmann, Otto: Arch. f. path. Anat. **13**:501-505, 1858.
37. Gerhardt, C.: Würzburger med. Ztschr. **3**:141-149, 1863.
38. Ponfick: Arch. f. path. Anat. **50**: 623-633, 1870.
39. Litten, M.: Virchows Arch. f. path. Anat. **73**:289-321, 1875.

bowel affected is thrown into anemic contracture for several hours, that it then dilates and hemorrhagic infarction results. They observed that if the arteries supplying a loop much more than 5 cm. long were thus closed the result was hemorrhagic infarction with necrosis. Although the anastomoses were good they were insufficient, despite the fact that they were large in comparison with some of the trivial anastomoses which in external parts respond effectively to the call for a collateral circulation to far larger areas. Mall and Welch accepted the theory of von Frey [34] that pulsating force is necessary to prevent speedy blocking of the veins and capillaries with red cells in carrying on artificial circulation with defibrinated blood through living organs. They believed the absence of pulsation was the factor of first importance in the causation of hemorrhagic infarction following arterial embolism.

Erlanger and Gasser [40] believed that diapedesis may be due to mere slowing of the stream rather than to the absence of pulsation as reported by Mall and Welch.[34] The latter reported gross findings of thickened intestinal wall in occlusion of the mesenteric artery. In addition, they stated "The lumen of the intestine contains black tarry blood. There is bloody fluid in the peritoneal cavity and usually a fibrinous, sometimes a fibrino-purulent exudate on the peritoneum covering the infarction." Ackman [41] found the superior mesenteric artery involved by emboli more often than the inferior. He stated that this was because it was more open, nearer the heart and more oblique.

Obstruction Due to Intestinal Strangulation.—In intestinal obstruction in which strangulation is present, both arteries and veins may commonly be obstructed. Payr [42] cited the case of a woman aged 39 in whom at operation the bowel was found strangulated by an adhesive band. After resection of 265 cm. of intestine the patient recovered. About 2 liters of fluid was found in the peritoneal cavity. Payr discussed the mechanism by which this exudate was formed and attributed it to the edema secondary to vascular obstruction. Bayer [43] believed that the presence of peritoneal exudate is of importance in the diagnosis of acute intestinal obstruction. Kader [44] discussed the edema and venous engorgement in intestinal obstruction and reported experiments with strangulated intestinal loops in dogs. Braun [45] reported three cases of volvulus of the sigmoid flexure and collected thirty-one

40. Erlanger, J., and Gasser, H. S.: Ann. Surg. **69**:389-421, 1919; Am. J. Physiol. **49**:151-173, 1919.

41. Ackman, F. D.: Canad. M. A. J. **25**:657-663, 1931.

42. Payr, E.: Arch. f. klin. Chir. **67**:181-201, 1902.

43. Cited by Payr.[42]

44. Kader, B.: Verhandl. d. deutsch. Gesellsch. f. Chir. **21**:242-248, 1891.

45. Braun, H.: Verhandl. d. deutsch. Gesellsch. f. Chir. **21**:368-399, 1891.

instances from the literature. In two of his cases a considerable amount of peritoneal exudate was found at operation; no mention was made in this regard concerning the third case. He attributed this fluid to venous stasis and believed that it was similar to the hernial fluid in strangulated external hernia. He mentioned having seen similar fluid in strangulation due to Meckel's diverticulum.

Scott and Wangensteen [46a] performed extensive experiments on obstruction due to strangulation. In dogs, the blood supply to loops of intestine almost 5 feet (1.5 meters) long was obstructed in four ways: (1) encirclement of the entire loop by a ligature, (2) ligation of an artery, (3) ligation of a vein and (4) ligation of both arteries and veins. The average length of life in the four groups was sixteen, twenty, five and one-half and nineteen hours respectively. Scott and Wangensteen [46b] also found that the most marked fall of blood pressure occurred following venous ligation. Injection of the peritoneal exudate [46c] in amounts of from 20 to 185 cc. into the leg veins of other dogs produced no ill effects unless the strangulated loops were very necrotic or had ruptured. Scott and Wangensteen [46c] completed their studies by measuring the losses of blood by hemorrhage into the gut and peritoneal cavity. In venous obstruction leading to death the total loss of blood averaged 4.1 per cent of the body weight. They stated: "The peritoneal cavity usually contained a bloody serous fluid. Hemoglobin content was usually less than 10 per cent, but the total protein content was always that of the animal's own blood plasma."

REPORT OF CASES

CASE 1.—*Chronic thrombosis of the portal vein with superimposed acute thrombosis of the mesenteric vein; gangrenous infarction of the small intestine; resection of 241 cm. of intestine; death.*

A teacher aged 48 entered the hospital Aug. 26, 1935, because of jaundice. Three weeks and one week prior to this she had had attacks of severe griping pain in the abdomen, and for a week, diarrhea. Roentgen examination August 5 indicated a duodenal ulcer. The jaundice was accompanied by slight pain in the epigastrium. There was no fever; the white blood cell count was 9,000; the hemoglobin, 91 per cent; the red blood cell count, 4,900,000. The urine contained bile; the van den Bergh reaction was immediate, direct, and on cholecystographic examination the gallbladder appeared to be normal and without stone. The abdominal distress and jaundice disappeared, and the patient was discharged October 3 with a diagnosis of duodenal ulcer and catarrhal jaundice and given antacid powders.

Six days later she returned complaining of severe abdominal pain of five days' duration that was steadily increasing in severity. One day later she was seen by the surgical service. She had had no bowel movement for two days, and an enema was returned with a hard clay-colored stool and no blood. The abdomen

46. Scott, H. G., and Wangensteen, O. H.: Proc. Soc. Exper. Biol. & Med. **29**: (*a*) 424-427; (*b*) 428-431; (*c*) 559-561; (*d*) 748-751, 1932.

was distended and contained fluid with shifting dulness. There was no marked tenderness. The pulse rate was normal. The heart appeared normal. There was no jaundice. The temperature was 99.8 F.; the white blood cell count, 19,000; the differential, 88 per cent polymorphonuclear neutrophils. There was no preoperative red blood cell count. The urine contained albumin. The blood pressure was 136 systolic and 90 diastolic, and two hours later it was 115 systolic and 80 diastolic. October 10, at 2:15 p. m., the abdomen was opened in the midline under ethylene anesthesia, and about 200 cm. of the jejunum and upper part of the ileum was found gangrenous; 230 cc. of a bloody fluid was aspirated from the peritoneal cavity (table 1). The gangrenous intestine was resected, the ends were closed by inversion sutures, and a lateral anastomosis was made. The upper end of the gangrenous part of the bowel was so near to the ligament of Treitz that mobilization for this anastomosis was difficult. The cut portion of the mesentery bled only slightly, and clots were expressed from the veins like dry tooth-paste from a tube. The abdomen was closed.

At the end of the operation the blood pressure was 70 systolic and 60 diastolic and later unreadable. Before the patient left the operating table, but after 900 cc. of physiologic solution of sodium chloride had been given intravenously, the hematocrit reading was 61 and the hemoglobin 143 per cent. The patient was then given a transfusion of 500 cc. of citrated blood; the blood pressure rose to 136 systolic and 90 diastolic, and an hour later that evening the hematocrit reading was 58 and the hemoglobin 115 per cent. The next morning, at 8 a. m., the blood pressure had fallen to 100 systolic and 76 diastolic, the hematocrit reading was 60 and the hemoglobin 126 per cent. The patient was now unconscious; 900 cc. of physiologic solution of sodium chloride was given intravenously, and at 10:30 a.m. the pressure had fallen to 94 systolic and 70 diastolic and soon thereafter was unreadable. The pulse rate averaged 140 to 184, and the patient vomited dark red fluid in large amounts, estimated at 2 liters before death, which occurred twenty-three hours after operation. The temperature an hour before death was 108.6 F. by rectum, and ten minutes before death the hematocrit reading was 58 and the hemoglobin was 127 per cent.

Pathologic Examination of Surgical Specimen.—The segment of bowel was 240 cm. long; the average circumference was 8 cm., and the weight empty was 990 Gm. The contents were bloody and weighed 470 Gm. There were 18 cm. of relatively normal wall at the lower end and 9 cm. of normal bowel at the upper end. Section showed gangrene and distention of blood vessels with red blood cells around the periphery of the gangrenous region.

Necropsy.—Organized thrombosis of the portal vein and of its pyloric branch, possibly from duodenal ulcer, with recent propagating retrograde thrombosis of the entire portal system was found; also hemorrhagic infarction of the distal 10 cm. of the remaining jejunum; fibrous periduodenitis with traction deformity of the duodenum; hemorrhagic fibrinous ascites (590 cc. of spontaneously clotting fluid); blood in the alimentary canal from the mouth to the colon, and acute passive hyperemia of the spleen and intestines. Except for a patent foramen ovale, the heart was normal. The portal system was almost entirely occluded by thrombi. The two main intrahepatic branches of the portal vein were thin-walled and empty. Just before their union to form the main portal vein each became completely occluded by an old organized white thrombus, which extended down 5 cm. to the point where the portal vein is formed by the union of the superior mesenteric and splenic veins. The first 5 cm. of the pyloric vein was filled by an organized white thrombus continuous with that in the portal vein. Beyond this

point the pyloric vein was filled by a recent soft red thrombus similar to that found elsewhere in the portal system. The first portion of the pyloric vein was buried in dense fibrous tissue stained with hemosiderin and lying beneath the oval atrophic area in the duodenum. At numerous places behind the duodenum and in close relation to the pyloric vein, portal vein, hepatic duct and hepatic artery were masses of dense fibrous tissue. The splenic and the superior and inferior mesenteric veins were dilated and completely filled with red antemortem thrombi except that at a point opposite the most proximal portion of the sigmoid colon the thrombus of the inferior mesenteric vein suddenly stopped. Of the entire portal system, the left gastro-epiploic vein alone was not thrombosed. The spleen weighed 450 Gm. but was not boggy. An analysis of the peritoneal fluid found at necropsy is shown in table 1.

TABLE 1.—*Comparison of the Results of Chemical Analysis of the Blood Plasma and of the Peritoneal Fluid found at Operation and at Necropsy*

	Amount, Cc.	Hemoglobin, per Cent	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin / Globulin Ratio	Sugar, Mg. per 100 Cc.	Sodium Chloride, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.
Blood plasma after operation	...	143*	4.8	3.1	1.1	2.9	112	575	38
Peritoneal fluid†									
At operation	230	40	3.0	2.1	0.7	2.9	215	577	36
At necropsy	590	..	2.8	2.4	0.4	6.0	110	670	66

* In whole blood.
† The peritoneal fluid is somewhat more dilute than blood plasma in total protein content but is not a mere transudate.

The chronic obstruction of the portal vein in this patient is of interest in view of the reports of de Jong,[11] Sprengel[12] and Simonds.[13] Besides the peritoneal exudate, the edema of the bowel wall, splenic enlargement and extensive vomiting of bloody fluid afford possibilities for an extensive loss of circulating fluid. This is the only case in the series in which studies of the blood concentration and blood pressure were made.

CASE 2.—*Thrombosis of the portal and mesenteric veins; death; enormous collection of peritoneal fluid at necropsy.*

A housewife aged 48 entered the clinics July 24, 1935. She complained that she had had severe cramplike pain in the abdomen for one week, accompanied by frequent vomiting. The pain was of sudden onset. The bowels had moved daily since the onset, and shortly after admission she had a bloody stool. She noted a gradual distention of the abdomen. For some time she had had swelling of the ankles. She had a soft systolic murmur at the cardiac apex, distention of the abdomen with some fluid, no localized tenderness or mass and very little or no peristaltic sound. The white blood cell count was 30,000 the day of admission and 15,000 two days later. The red blood cell count and hemoglobin were 4,100,000 and 85 per cent the day of admission and 3,800,000 and 74 per cent

two days later. The urine contained albumin and casts. The Wassermann reaction was negative. Roentgen examination of the intestinal tract showed delayed passage of barium sulfate through the small bowel and irregular incomplete filling of the transverse colon. The blood pressure was 138 systolic and 96 diastolic; the pulse rate averaged 110, and the temperature was 97.2 F. on admission, reached a peak of 100.6, but showed a tendency to stay below normal. The patient grew weaker and died three days later after emesis of a large amount of dark bloody fluid.

Necropsy.—There was an occlusive thrombosis of the portal vein with propagating thrombosis of the splenic and mesenteric veins and with hemorrhagic infarction of the jejunum, transverse colon, related mesentery and omentum. There was 4,000 cc. of blood-stained fluid in the peritoneal cavity. Analysis of this fluid gave: hemoglobin, 5 per cent (Sahli); total protein, 2.4 Gm. per hundred cubic centimeters; nonprotein nitrogen, 30 mg.; sugar, 126 mg., and sodium chloride, 656 mg. The albumin-globulin ratio was 7.5. There was a sharp transition just below the ligament of Treitz between normal and dark hemorrhagic bowel. Below this was 65 cm. of necrotic bowel, at the lower end of which the line of demarcation was less sharp than at the upper end. About 10 cm. of the transverse colon was also infarcted. Histologic examination of the thrombus in the portal vein showed it to be older than the thrombi elsewhere, the appearance of loss of hemoglobin suggesting that it had been present for more than two weeks.

The loss of a large amount of fluid somewhat similar to blood plasma although more dilute in protein content is of possible importance. However, the rate at which this fluid was lost is of prime significance and is unknown. It may have been too slow to have altered the picture appreciably.

CASE 3.—*Thrombosis of the superior mesenteric and portal veins; abdominal pain of four days' duration; appendectomy; death fourteen hours later; at necropsy, infarction of 80 cm. of small intestine; blood-stained peritoneal exudate at operation and at necropsy.*

A colored dentist aged 39 entered the clinics Dec. 30, 1929, and died thirty-six hours later. He complained of severe pain in the upper part of the abdomen of four days' duration with vomiting, constipation and a temperature of from 99 to 99.6 F. each day. The abdomen was soft and slightly distended, contained no fluid and was somewhat tender. The heart was normal. The next day the abdomen was more rigid, and a mass was palpable in the right lower quadrant. The Wassermann reaction was 4 plus. The blood pressure was 165 systolic and 120 diastolic. The white blood cell count was 11,000 on admission and 19,000 just before operation. The red blood cell count was 5,100,000 just before operation. The urine contained albumin and casts.

The day after admission a McBurney incision was made. A large amount of blood-stained fluid was found in the peritoneal cavity. The bowels were matted about a small abscess, around the appendix (no cultures were taken). Appendectomy was done. No note was made of any general abdominal exploration. Pathologic examination revealed healed appendicitis only.

Twelve hours postoperatively the pulse rate was 140 and the blood pressure 84 systolic and 74 diastolic. Later the pressure fell to 60 systolic, and the diastolic pressure was not readable. The patient vomited 200 cc. of dark bloody fluid and was given a blood transfusion. Just before death the temperature rose to 106.4 F.

Necropsy.—The observations were thrombosis of the superior mesenteric, portal, splenic, short gastric and left gastro-epiploic veins with gangrenous infarction of 80 cm. of the jejunum and ileum; acute generalized serofibrinous and hemorrhagic peritonitis (no cultures were taken); acute hemorrhage into the small intestine, duodenum and stomach; slight enlargement of the heart. There was 100 cc. of bloody fluid in the peritoneal cavity. The gangrenous bowel was covered with fibrinous exudate. The mesenteric arteries were clear. There was bloody fluid in the stomach and small intestine. The spleen was small (weight, 90 Gm.).

The venous thrombosis was overlooked at operation. Its origin may have been on a syphilitic basis. The peritoneal exudate and hemorrhage into the intestines were typical of vascular occlusion.

CASE 4.—*Embolism of the superior mesenteric artery with gangrene of the intestines on the basis of vegetative aortic endocarditis; perforations found at operation; death.*

A clerk aged 47 entered the clinics Dec. 21, 1934, and died six hours after admission. He complained of cramps in the lower part of the abdomen, nausea, vomiting and low grade fever of two and one-half weeks' duration. Systolic murmers were heard at both the apical and aortic regions of the heart. The abdomen was somewhat distended and rigid but not especially tender. There was no rebound tenderness. The white blood cell count was 13,000; the red blood cell count 4,800,000. The urine contained casts and a trace of albumin. Roentgen examination revealed distended intestinal loops. The pulse rate was 100, and the temperature never exceeded normal. The blood pressure was 142 systolic and 88 diastolic. At operation the peritoneal cavity contained "a large amount" of blood-stained serous fluid, and recent fibrinous adhesions were present. The bowel was gangrenous from the jejunum to the ascending colon and was so friable that it broke in at least seven places as it was lifted gently. The limits of the gangrenous area could not be reached, so the abdomen was closed. Rapid failure and death occurred four hours after operation.

Necropsy.—Embolism of the superior mesenteric artery was found, with gangrene of most of the jejunum, ileum, appendix, cecum and 10 cm. of the ascending colon (285 cm. of gangrenous bowel); also thrombotic vegetative aortic endocarditis. There was 500 cc. of foul-smelling bloody fluid in the peritoneal cavity. Three centimeters from its origin the superior mesenteric artery was unchanged. Here it gave off a branch which supplied the upper end of the jejunum. This branch was normal. Four centimeters distal to its origin the superior mesenteric artery was occluded by a mixed red and gray thrombus. The proximal end of the thrombus was pointed; more distally it filled the artery and had ramifications into all the branches for a distance of several centimeters. Beyond this the branches were empty and normal. The inferior vena cava and the mesenteric, splenic and portal veins were unchanged. Histologic examination of the mesentery showed all the veins to be filled with blood. Thrombi were present in some of the arteries, and one of the thrombi was almost completely organized. Cross-section of the superior mesenteric artery showed it to be completely occluded by an antemortem thrombus.

The exact amount of peritoneal exudate found at operation was uncertain because of the immediate perforations. The gangrenous

bowel was not edematous or as markedly engorged with blood as in instances of venous occlusion.

CASE 5.—*Occlusion of the inferior mesenteric artery associated with cardiac mural thrombi; no symptoms referable to the abdomen; no operation; lesion found at necropsy; no peritoneal exudate.*

A printer aged 60 entered the clinics April 18, 1933, and died sixteen days later. His complaints were: dyspnea, precordial pain, profuse sweating and hemoptysis of one months' duration. He showed emaciation, enlarged heart and an enlarged liver and had râles in the lungs and high blood pressure (190 systolic and 135 diastolic). There were albumin, casts and pus in the urine. The blood two days after admission showed 16,000 white cells, 5,000,000 red cells and 95 per cent hemoglobin (Sahli); no studies were made thereafter. The patient experienced burning on urination the last seven days of life and severe precordial pain the last twenty-four hours; no symptoms were referable to the abdomen. The temperature was never higher than 101.6 F.

Necropsy.—The observations were: syphilitic aortitis; coronary arteriosclerosis; recent thrombotic occlusion of the circumflex branch of the left coronary artery with a mural thrombus of the left ventricle; saccular aneurysm of the abdominal aorta with mural thrombi; obliteration of the inferior mesenteric and renal arteries by thrombi, and a small infarct of the spleen. There was no exudate, and the portal vein and its branches and the intestines were normal.

This case may represent a terminal embolism of the mesenteric artery or an occlusion in which collateral circulation prevented infarction. Thus, the absence of peritoneal fluid is of little significance and is indicative of the mild degree of the occlusion rather than of its type.

CASE 6.—*Mural thrombi of the left ventricle with multiple embolic occlusions including occlusion of the superior mesenteric artery; death forty hours after sudden onset of severe epigastric pain; infarction of cecum and small intestine and 250 cc. of peritoneal fluid present at necropsy.*

An unmarried woman aged 42 entered the clinics Sept. 5, 1930, and died seventeen days later. She had suffered from dyspnea on exertion for two years and from pains in the calves on walking for three years. She was obese, with a pulse rate of 120, an enlarged heart and an enlarged liver and her blood pressure was 200 systolic and 140 diastolic.

On the sixth day of her stay in the hospital painful cyanosis developed in the left foot and râles were heard at the base of the left lung. A mental disturbance occurred at the same time. September 20, in the evening, she suddenly had exceedingly severe epigastric pain of cramplike nature, which continued and was not relieved by morphine. The blood pressure was 210 systolic and 148 diastolic. Next morning abdominal auscultation revealed peristalsis; the abdomen was soft and not distended and there was no localized tenderness. Sixteen hours after the onset the blood pressure had fallen to 120 systolic and 90 diastolic. Nine hours later it was 140 systolic and 95 diastolic. Death occurred with symptoms of shock forty hours after onset of the abdominal pain. On admission there had been albumin and pus cells in the urine, a red blood cell count of 3,800,000 and a white cell count of 13,000; five hours after onset of the abdominal pain the white cell count was 31,000. The temperature averaged from 100 to 101 F. at death.

Necropsy.—The observations were: arteriosclerotic changes; mural thrombi in the left ventricle; generalized fibrinopurulent peritonitis secondary to thrombosis of the superior mesenteric artery with early infarction of the cecum and small intestine; cortical infarct of the kidney; massive infarct of the spleen; healed peptic ulcer, and superficial gangrenous necrosis of the left great toe. The peritoneal cavity contained about 250 cc. of turbid fluid. The bluish green infarcted intestine was covered by a fibrinous exudate. The spleen weighed 220 Gm.

The extremital, superior mesenteric, renal and splenic arterial occlusions were probably on the basis of emboli from mural thrombi in the left ventricle. Despite the possible forty hours' duration of the superior mesenteric infarction, only 250 cc. of peritoneal exudate was found at necropsy, and despite complete infarction of the spleen, it was little enlarged.

CASE 7.[47]—*Occlusion of mesenteric, celiac, splenic, hepatic and left gastric arteries; resection of 269 cm. of small bowel; death; moderate peritoneal exudate.*

A housewife aged 36 entered the clinics March 18, 1932, and died a week later. She complained of nausea, vomiting and generalized abdominal pain of one week's duration. She had had a previous attack one month before. There was a soft systolic murmur at the base of the heart and a mass in the lower part of the abdomen extending up almost to the umbilicus. Six days later the abdomen was markedly distended and silent on auscultation. The blood pressure was 150 systolic and 75 diastolic. The white blood cell count was 14,000 on admission and 44,000 five days later. The red cell count was 3,000,000 on admission and the same five days later.

At laparotomy about 350 cc. of serosanguineous fluid was found in the peritoneal cavity. Almost the entire small intestine was gangrenous, ranging in color from black to dusky red, and 269 cm. of it was resected. The cut mesentery did not bleed. A gun-barrel fistula was produced with the open ends of the ileum and jejunum. The blood pressure at the start of the operation was 118 systolic and 80 diastolic and at the end was 94 systolic and 65 diastolic.

A blood transfusion was given immediately after the operation. The patient vomited over a liter of dark brown fluid and died sixteen hours after the operation.

Necropsy.—Thrombosis of the mesenteric, celiac, splenic, hepatic and left gastric arteries and their branches and of the left middle suprarenal artery was found, apparently resulting from embolism from a mural thrombus on an atheromatous plaque in the descending thoracic aorta and old and recent anemic infarcts of the spleen; also were found gangrene of a portion of the remaining jejunum; recent anemic infarcts of the kidneys, and hemorrhage in the left adrenal gland. There was about 200 cc. of slightly turbid fluid in the peritoneal cavity. The spleen was enlarged (weight, 260 Gm.).

The extensive resection is of interest. The vomiting and the splenic enlargement are additional sources of loss of fluid in this patient.

47. This case has been reported by H. E. Haymond (Surg., Gynec. & Obst. **61**:693-705, 1935).

CASE 8.—*Arterial occlusion with infarction of 4 feet (1.2 meters) of small intestine; abdominal pain, vomiting and bloody stools with onset three days before operation; peritoneal cavity contained a liter or more of clear fluid; resection and side to side anastomosis; recovery.*

A boy aged 16 had been treated in the clinic intermittently over a year for chronic osteomyelitis of both femurs and tibias with amyloidosis. He entered the hospital Dec. 15, 1933, complaining of cramplike abdominal pain, vomiting of forty hours' duration, and several bloody stools. The abdomen was tender in the right lower quadrant, and rigidity and rebound tenderness were present. The white blood cell counts ranged between 14,000 and 19,000; no red cell count was made except just before operation when it was 5,280,000 with the corresponding hemoglobin 86 per cent. The urine, as previously, contained albumin. The highest preoperative temperature was 99.6 F.

At operation, December 16, the peritoneal cavity contained a liter or more of clear straw-colored fluid. The ileum was dusky red to light purple over a length of 4 feet. No definite gangrene was present. The normal bowel above and below this region contained blood. The involved area was resected and a side to side anastomosis performed. The specimen showed necrosis of the mucosa, clots in the arteries and acute enteritis.

Following the operation there were no signs of shock; occasionally there was pain, and minor amounts of blood were noted in stools; diarrhea continued for five weeks. The patient was in good condition twenty months later.

It was believed that there were small infarcts in the peripheral mesenteric arteries. The absence of demonstrable cardiac lesions such as are the usual source of these emboli makes this supposition unproved.

CASE 9.—*Recent occlusion of the superior mesenteric artery associated with infarction of the myocardium and carbon monoxide poisoning; intestine normal despite arterial occlusion; no peritoneal fluid.*

A housewife aged 67 entered the clinics Jan. 28, 1934, and died the next day. The relatives stated that she had suffered from coma, vertigo, headaches, nausea and vomiting due to carbon monoxide poisoning. Examination revealed a woman in coma, unable to answer questions, and with generalized arteriosclerosis, hypogastric hernia and ulcers of the leg. The heart began to fibrillate, and death occurred soon after admission before treatment could be instituted. The white blood cell count was 15,000; the red blood cell count, 4,300,000; the hemoglobin, 85 per cent. The urine was normal. The blood showed 3 per cent carbon monoxide saturation. The pulse rate averaged from 120 to 130; the temperature, from 100 to 102 F.; the blood pressure was not observed.

Necropsy.—Postmortem examination showed: cerebral arteriosclerosis with softening; a cherry-red color of the blood; thrombosis of the left posterior tibial artery; a recent occluding antemortem thrombus of the superior mesenteric artery; a healed infarct in the wall of the left ventricle and in the left interventricular septum. The intestine was normal, and there was no free peritoneal fluid.

It is uncertain as to whether the antemortem clot in the superior mesenteric artery was of such recent origin that there was not time for infarction. This case is included in this series only for completeness and the absence of both infarction and fluid is of little interest for this study.

Another case of intra-abdominal arterial occlusion will be mentioned at this time although it does not strictly come in the group of cases discussed here:

A man aged 57 died four days after a Polya resection for carcinoma of the stomach. Forty hours before death the blood pressure was 80 systolic and 68 diastolic. It later fluctuated between 90 systolic and 56 diastolic and 108 systolic and 68 diastolic, and the patient presented the general appearance of shock throughout the postoperative period. Necropsy revealed extensive pneumonia, and the celiac artery was thrombosed at its point of origin from the aorta for a distance of 8 mm. Beyond this point it was not thrombosed, and its branches were clear except the left branch of the left gastric artery, which had been tied with a catgut ligature and contained a thrombus 1 cm. long at that point. There was no sign of necrosis in the remaining parts of the stomach or intestine, no sign of infarction of the mesentery and no peritoneal fluid.

TABLE 2.—*Summary of Findings in Nine Cases of Mesenteric Vascular Occlusion*

Case	Sex	Age	Duration in Days	Vomiting Before Operation	Abdominal Distention	White Blood Cell Count	Temperature, F.	Peritoneal Exudate: Operation	Peritoneal Exudate: Physical Examination	Peritoneal Exudate: Operation	Peritoneal Exudate: Necropsy	Outcome
						Venous Occlusion						
1	F	48	7	0	+	19,000	100.0	+	+	+	+	Death
2	F	48	10	+	+	30,000	97.2	0	+	0	+	Death
3	M	39	5	+	+	11,000	99.6	+	0	+	+	Death
Average or total		45	7	2	3	20,000	98.9	2	2	2	3	
						Arterial Occlusion						
4	M	47	18	+	+	13,000	98.4	+	0	+	+	Death
5	M	60	?	0	0	16,000	101.6	0	0	0	0	Death
6	F	42	2	0	0	31,000	101.0	0	0	0	+	Death
7	F	36	14	+	+	44,000	101.0	+	—	+	+	Death
8	M	16	3	+	—	19,000	99.6	+	—	+	0	Recovery
9	F	67	?	+	—	15,000	101.0	0	—	—	0	Death
Average or total		45	9	4	2	25,000	100.4	3	0	3	3	
Grand average		45	8	6	5	22,000	99.9	5	2	5	6	Mortality, 80%

ANALYSIS OF CASES

Of the nine cases of occlusion, three were venous and six arterial in origin (67 per cent arterial). This agrees with the preponderance of cases of arterial occlusion found by other authors, Jackson, Porter and Quinby [27] reporting 61 per cent, Trotter [31] 53 per cent, Boyce and McFetridge [1] 69 per cent and Elliot [28] 78 per cent. Five of the patients, as shown in table 2, were females (55 per cent), while Boyce and McFetridge [1] found 77 per cent females and Jackson, Porter and Quinby [27] 64 per cent males. Six of the patients were between 36 and 48 years of age, the average being 45 years. This predilection for late middle age agrees with the observations of previous workers.[48] The

48. Boyce and McFetridge.[1] Jackson, Porter and Quinby.[27]

average duration of symptoms in the seven patients on whom adequate information is available was eight days. Jackson, Porter and Quinby,[27] on the other hand, found that over half their patients had symptoms of less than three days' duration. Vomiting was present in six of nine patients and abdominal distention in five of seven on whom adequate data are recorded. Loop [29] noted bloating of the abdomen, and Jackson, Porter and Quinby [27] noted that 78 per cent of their patients had distention. Fluid in the peritoneal cavity was noted on physical examination of two of the three patients seen by me, and its absence was specifically noted in three others. At operation, however, fluid was found in all the patients, and at necrospy, in six of the nine. Boyce and McFetridge [1] and others have noted the mildness of the fever in this condition. Operation was performed on five patients, with one recovery. Boyce and McFetridge [1] and Loop [29] each reported a series of nine operations with one recovery. Jackson, Porter and Quinby [27] found forty-seven reported operations with four recoveries (94 per cent mortality). Meyer [30] collected reports of forty-three resections with a mortality of 32.6 per cent. In my series all of the patients operated on died, and as it is difficult to make the diagnosis without operation or necropsy it is impossible to know whether any patient not operated on recovered and therefore such patients were omitted from this study.

Eight of the patients were examined post mortem. At necropsy the upper end of the gangrenous portion was separated much more abruptly from the adjacent normal portion of the bowel than the lower end, where the shading was gradual in all three of the cases of venous occlusion. In one case of arterial occlusion (case 7, in the report of which mention is made of this fact) the juncture is more gradual at the upper than at the lower end. Elliot [25] reported diffuse shading at both ends in a case of his series. Reich [28] found, contrary to the condition existing in my series, that the sharpest line of demarcation in both arterial and venous types of occlusion was at the lower end of the gangrenous segment. In Elliot's [25] second case of arterial occlusion perforation occurred as in my case 4. It is quite possible that perforation is more common in the arterial type. In the group of cases reported by Boyce and McFetridge [1] all occlusions involved the superior mesenteric vessels, which was true for my series except in one case.

In two of the cases (5 and 9) there was no infarction of the intestine despite the presence of definite antemortem thrombi in the superior mesenteric artery. It is possible that this occlusion occurred so shortly before death or was accompanied by such adequate collateral circulation that infarctive changes did not result. The occlusion in case 5 was in the inferior mesenteric artery, and Mall and Welch,[34] as already mentioned, have stated that this vessel can sometimes be obliterated without serious effect.

The other seven cases lend themselves to analysis concerning the possibility that secondary surgical shock is a factor. Six of the seven patients died, and secondary surgical shock was possibly a factor in their deaths. Unfortunately, the studies of their blood pressure were incomplete. Except for the patient in case 1 (considered in the following paragraph) few patients had blood pressure readings within several days of death. In case 3 the blood pressure fell to 84 systolic and 74 diastolic twelve hours after operation. In case 4 the blood pressure fell rapidly during and after operation. In case 6 the systolic blood pressure fell from a previous level of 210 to 140 twenty-five hours after the onset of symptoms, but during the ensuing fifteen hours no readings were taken.

In none of the cases were the studies of the blood adequate to enable one to determine the presence of hemoconcentration except in case 1. In this instance there was definite concentration of the blood, with hemoglobin 143 per cent and the hematocrit reading 61 despite the fact that there had been no previous vomiting. Studies of the blood pressure showed a definite drop the morning after operation, with readings of 94 systolic and 70 diastolic three hours before death.

In these patients, plasma-like fluid and blood were lost not only into the peritoneal cavity but into the wall of the bowel, the mesentery, sometimes the spleen and the intestinal lumen. As a result of the escape of fluid and blood into the latter, melena and vomiting may occur. In all three instances of venous thrombosis there was marked vomiting of bloody fluid. In one case of arterial occlusion (7) the patient vomited a liter of "dark brown" fluid. Transfusion of blood was administered in two cases (1 and 7) with recovery in neither instance.

COMMENT

A study of cases and of the literature indicates that mesenteric vascular occlusion is a disease of middle age affecting persons of both sexes and often of insidious onset. Preexisting cardiac disease is frequently present with the arterial embolic types and vague abdominal distress and occasional occlusion of the portal vein with the venous types. The local findings of rigidity and tenderness are less than the pain would indicate. Distention is often observed, and free fluid should be searched for. Vomiting and melena are sometimes present, and the signs of intestinal obstruction are a feature except that auscultation of the abdomen frequently reveals a preternatural lack of sounds. At operation or necropsy the infarction is usually hemorrhagic, even in the arterial type, and this is due to inflow of blood from the collateral vessels as shown by Mall and Welch.[34] The intestinal loop contains less gas and more fluid than in most other types of obstruction: the

bowel and mesentery are boggy and edematous, and there is considerable free fluid in the abdominal cavity. This fluid is apt to be more abundant in venous occlusion, while perforation of the intestine is more apt to follow arterial obstruction. Despite early operation the mortality is high and gangrene spreads after resection.

The amount of local blood lost into the infarcted organs and into the peritoneal cavity has been shown experimentally to be sufficient to account for the death of the animals in question. In clinical cases, few quantitative estimations of this fluid loss have been recorded. Some observers, for instance, Moon,[49] have realized that shock may be a factor in death from this condition. In certain cases it is quite certain that the loss of fluid is not sufficient to account for death. Secondary peritonitis and the intestinal obstruction itself are lethal factors of importance here as they are in other conditions.

SUMMARY AND CONCLUSIONS

The literature on occlusion of mesenteric blood vessels is reviewed with special reference to the subject of secondary surgical shock. Except for very occasional citation, this aspect of the condition has received little clinical notice either in reports or treatment. On the other hand, the literature on experimental occlusions indicates that secondary surigcal shock from loss of a bloody plasma-like fluid into the peritoneal cavity or of blood into the wall or lumen of the intestine may be a major factor in death in these cases.

Nine cases of mesenteric vascular occlusion are reported. Most of these were observed before interest in the possible presence of shock was aroused and were not adequately investigated from this standpoint. One of the purposes of this paper is to enter a plea for more adequate study of such cases from the standpoint of shock.

A study of these cases indicates that arterial occlusion is more common than venous, that most of the patients are in the upper middle age group, that vomiting is frequent, and often bloody in the venous type, that abdominal distention with fluid is frequently present, that the white blood cell count is elevated, that the temperature is only moderately high, that pain is greater than the accompanying rigidity and tenderness would indicate, and that the condition may simulate mild intestinal obstruction due to malignant disease.

Accompanying the hemorrhagic infarction of the intestines are edema of the bowel wall and mesentery, bloody fluid in the lumen of the bowel with melena and bloody vomitus, and an exudate of blood-stained plasma-like fluid in the peritoneal cavity.

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49. Moon, V. H.: Ann. Int. Med. **8**:1633-1648, 1935.

A QUANTITATIVE STUDY OF CELL GROWTH IN REGENERATING LIVER

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One of the most striking manifestations of the capacity of adult tissue to grow rapidly is seen in the process by which the liver restores itself to normal size following partial hepatectomy. After the removal of approximately 70 per cent of the liver of a white rat the remnant of the organ more than doubles in size in the course of the ensuing seventy-two hours.[1] This compares favorably with the increase in mass of a tissue culture of normal or sarcomatous fibroblasts growing under optimal conditions [2] and with the increase in size of the 8 to 10 day chick embryo.[3] It is considerably greater than the usual increase in the size of a malignant tumor in a corresponding length of time.[4]

Prior to 1931, experimental studies of this phenomenon were limited almost entirely to gross and microscopic examination of tissue during restoration and were at best only semiquantitative. The literature of this period has been reviewed very thoroughly by Fishback,[5] and so we shall in no wise attempt a complete review of the subject except so far as the nature and rate of this growth process are concerned.

Ponfick [6] was the first to observe recreation of liver tissue in rabbits following partial hepatectomy, and his observations were later confirmed by von Meister.[7] Milne [8] ligated the branches of the portal vein and hepatic artery to certain lobes of the liver in rabbits and cats and observed compensatory hypertrophy of the other lobes. Rous and Larimore [9]

From the Medical Laboratories of the Collis P. Huntington Memorial Hospital.

1. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.
2. Carrel, A., and Ebeling, A. H.: J. Exper. Med. **48**:105, 1928.
3. Murray, H. A.: J. Gen. Physiol. **9**:29, 1926.
4. Bashford, E. F.: Scient. Rep. Imp. Cancer Research Fund **4**:197, 1911.
5. Fishback, F. C.: Arch. Path. **7**:955, 1929.
6. Ponfick, E.: Virchows Arch. f. path. Anat. (supp.) **138**:81, 1894.
7. von Meister, V.: Beitr. z. path. Anat. u. z. allg. Path. **15**:1, 1894.
8. Milne, L. S.: J. Path. & Bact. **12**:287, 1908.
9. Rous, P., and Larimore, L. D.: J. Exper. Med. **31**:609, 1920.

likewise ligated the portal vein to the main lobe of the liver in rabbits. They noted beginning proliferation after three days and estimated that the residual lobes had more than doubled in size after twelve days. The main lobe of the liver had atrophied in the meantime.

Fishback's [8] experiments were performed on dogs; under general anesthesia the pedicle to a given portion of the liver was clamped off and that portion removed. He removed between 65 and 70 per cent in most of his experiments, but there was no constant weight relationship between the various lobes. During the first three to five days, the sinusoids were engorged with an excessive blood flow, and the liver cells appeared swollen. Mitotic figures were never numerous and were seen from the second day to the fourth week. Many binuclear cells were seen. After two weeks, the liver was four-fifths recovered in size, and after from six to eight weeks a normal histologic picture had been reached.

Higgins and Anderson [1] made a very careful and complete study of the restoration of the liver in the white rat. Having established, on a large series of exsanguinated animals, the proportion of liver weight to body weight and its standard deviation, they performed partial hepatectomies in a series of rats and calculated the amounts of liver which were restored from the residual lobes at various periods of time.

They removed the bifurcate median and left lateral lobes under ether anesthesia. The animals were not made to fast before operation. On the first day after operation the animals received 20 per cent dextrose by mouth and then returned to a normal diet. In general these animals lost weight up to 15 Gm. each in the first ten or twelve days following operation, and it was demonstrated that the same weight loss takes place after simple laparotomy.

Their findings with regard to the amounts of liver restored in various intervals of time were expressed as percentages of the normal amount of liver expected in a group of animals of the same weight. At operation, 29.4 per cent of the liver was left in, as right lateral and caudate lobes. The percentages found postoperatively at various times follow: from sixteen to twenty-four hours, 45.3; twenty-four to forty-eight hours, 53.3; forty-eight to seventy-two hours, 70.6; four to seven days, 74.3; seven to fourteen days, 93; fourteen to twenty-one days, 102.3, and twenty-one to twenty-eight days, 110.9.

Since there was relatively little gain between the third and seventh days, they concluded that recovery of liver is not by uninterrupted continuous growth but cyclic.

They observed mitotic division in the latter part of the first day, but it was not active until the second and third days. The gain during the first twenty-four hours they attributed largely to nuclear and cytoplasmic hypertrophy.

The dry weights of the livers were estimated, and they discovered that during the first day only 33 per cent of the added material was water, although the water content of normal liver is over 70 per cent.

Up to this point, very little was understood about the stimulus to regeneration or about the limiting factor which causes growth to decelerate as the original liver mass is reached by the enlarging fragment. Mann and Magath [10] had shown that atrophy of the liver takes place when the portal blood is diverted from the liver by an Eck fistula. In 1931, Mann and co-workers [11] demonstrated that if a partial hepatectomy were done in a dog two or three months after making an Eck fistula the residual lobes regenerated little or not at all. Stephenson,[12] moreover, found that with partial ligation of the portal vein the final amount of liver restored was less than would be expected normally. Higgins, Mann and Priestley,[13] taking advantage of an anastomotic connection in the domestic fowl, were able to show that an increase in the portal blood flow causes restoration to be greater than in the presence of the normal portal flow.

These findings, coupled with the observation that soon after partial hepatectomy in the rat the sinusoids are markedly engorged with blood, led Higgins and Anderson [14] to conclude that restoration after partial removal is definitely correlated with the blood passing through the remaining hepatic parenchyma. They believe that the distention of sinusoids results in hypertrophy of the cells and that, with an occasional mitosis added, this largely explains all that is involved in hepatic restoration.

The effect of diet on the regeneration of hepatic tissue was investigated by Davis and Whipple.[15] They brought about liver necrosis by administering chloroform as an anesthetic or subcutaneously. Normal tissue was rebuilt most rapidly on a diet of meat or of carbohydrate and most slowly on a diet of fat. The rate of restoration was about the same in starved animals as in animals which were on a diet of fat. Opie and Alford [16] had shown previously that a fatty diet increased the susceptibility of liver to necrosis caused by carbon tetra-chloride, but that in phosphorus poisoning a diet of meat increased susceptibility to lesions more than did a diet of fat.

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10. Mann, F. C., and Magath, T. B.: Am. J. Physiol. **59**:485, 1922.
11. Mann, F. C.; Fishback, F. C.; Gay, J. G., and Green, G. F.: Arch. Path. **12**:787, 1931.
12. Stephenson, G. W.: Arch. Path. **14**:484, 1932.
13. Higgins, G. M.; Mann, F. C., and Priestley, J. T.: Arch. Path. **14**:491, 1932.
14. Higgins, G. M., and Anderson, R. M.: Arch. Path. **14**:42, 1932.
15. Davis, N. C., and Whipple, G. H.: Arch. Int. Med. **23**:711, 1919; **27**: 679, 1921.
16. Opie, E. L., and Alford, L. B.: J. A. M. A. **62**:895, 1914; **63**:136, 1914.

McJunkin and Breuhaus [17] studied the effect of intraperitoneal injections of macerated liver substance on the liver remnant following partial removal. They used the interesting method of studying regeneration on the basis of mitotic figures seen in a cross-section of the liver. They observed, on the whole, a great increase in mitotic figures in the animals that received the injections.

OBJECT

In the experiments which we shall now describe it was our purpose to study the rate of growth of liver tissue in the process of regeneration, or restoration, following partial hepatectomy in the albino rat. We wished to consider growth in the broadest sense as consisting of increase in mass (by assimilation of material) and of increase in cell number (presumably largely by mitosis; perhaps in part by amitotic nuclear division). Adolph [18] had shown that these two elements of the growth process may vary independently of each other with variation in temperature in the case of cultures of Paramecium.

It was necessary, therefore, to use a technic which would make it possible to estimate not only the mass of the liver at various times but also the number of hepatic cells in the liver. We have tried to make these estimations with as great accuracy as the material affords, by making conditions as basal as possible with respect to uniform fasting and complete exsanguination before the removal of specimens for examination.

METHODS

Animals Used.—The animals used in these experiments were inbred albino rats of the Slonáker strain. Most of them weighed between 110 and 180 Gm. at the time of operation. Males and females were kept separate. Their diet consisted of bread and milk unless otherwise specified. Food was withheld for twenty-four hours before operation, and for the same period before an animal was put to death.

Operations.—Partial hepatectomy was performed under ether anesthesia and with the customary sterile precautions. A midline incision was begun at the level of the xiphoid and extended down a convenient distance, usually 3 or 4 cm. With suitable retraction, the median and lateral lobes were delivered through the abdominal wall, and the pedicle containing the hepatic artery, bile duct and portal vein to these lobes was tied off with fine silk about 2 mm. above the point where these vessels separate from those to the posterior lobes. A small hemostat was applied distally to this ligature. The lobes were then allowed to fall back into the abdominal cavity until as much blood as possible had passed out of the liver through the hepatic vein. The pedicle was then cut between the ligature and the hemostat; the ligaments to these lobes were divided, and a heavy thread was passed around the lobes to be removed, and tied. The lobes were dissected off just distal to this tie and given to an assistant; any blood

17. McJunkin, F. A., and Breuhaus, H. C.: Arch. Path. **12**:901, 1931.

18. Adolph, E. L.: The Regulation of Size, Springfield, Ill., Charles C. Thomas, Publisher, 1931, p. 127.

which had been spilled was gently removed from the peritoneal cavity by gauze moist with sterile saline solution, and the operative wound was closed with two layers of silk sutures.

The immediate mortality was less than 5 per cent, and delayed mortality was nil except during a brief period when the rat colony was suffering from a respiratory infection.

When an animal was to be put to death, ether anesthesia was again induced, the abdominal wound was reopened, and the portal vein was tied off above the splenic vein, and the vena cava, above the renal vein. After the liver had become as bloodless as possible, the aorta was severed just above the diaphragm. The liver was then dissected out.

Preparation of Specimens.—At both operations and at autopsy the liver removed was further exsanguinated, a small amount of residual blood being removed from the hepatic and portal veins. The liver was then placed in a weighing bottle and weighed to the nearest milligram. About half of each lobe was then placed in a fixative for future microscopic examination and the weight of this fraction ascertained to the nearest milligram. The remainder of the liver, in most cases, was placed in concentrated sulfuric acid for determination of nitrogen.

Specimens were fixed in Zenker's fluid with 5 per cent glacial acetic acid or in solution of formaldehyde U. S. P. diluted 1 : 10 in 95 per cent alcohol. After fixation and washing, they were passed through alcohols, cleared in cedar oil and impregnated with paraffin for constant routine lengths of time. On removal from the paraffin oven, each specimen was wiped as dry as possible and weighed to the nearest milligram; the volume was then estimated by a method which will be described later. The specimen was then coated by rapid dipping in melted paraffin and kept until the two specimens (operation and autopsy) were obtained on the same animal. Each lobe was cut through the center to give a flat surface and embedded in paraffin so that this surface would be cut by the microtome knife. The specimens obtained at operation and autopsy on the same animal were embedded side by side so that they would be sectioned by the same stroke of the knife, and sections of measured thickness were cut, so that sections of all lobes as obtained at operation and autopsy were obtained. These were mounted on slides and stained with iron hematoxylin and eosin.

Estimation of Volumes of Specimens in Paraffin.—After specimens had been weighed on removal from the paraffin bath, they were weighed to the nearest milligram in paraffin oil and then embedded for cutting. Volume was calculated by this formula: $v = \frac{Wa - Wo}{S}$ in which v is the volume, Wa the weight in air, Wo the weight in oil and S the specific gravity of the oil. The formula is readily derived from Archimedes' principle.

Since a known fraction of the total liver had been removed and was represented by these specimens, it was possible to calculate the volume of the whole liver (assuming that it had all been through the fixation and embedding process), and this assumed total volume was used to calculate the number of hepatic cells in the entire liver from the number counted in a known microscopic volume.

During the process of reembedding specimens after determination of the volume they shrank a very slight amount as a result of being in hot paraffin for from three to five minutes. It was ascertained that specimens weighing 1 Gm. lost from 2 to 5 mg. during this process. No correction was made for

this very small error since all specimens could be supposed to have shrunk similarly and since our most significant results depend on the relative numbers of cells in different livers.

Estimation of Number of Cells by Microscopic Examination.—A carefully calibrated area of 1.6 sq. mm. in each section was chosen, and the thickness of each section was verified by a micrometer scale on the fine adjustment of the microscope. All hepatic cell nuclei were counted which impinged at all on the section in this area. This count represents, obviously, the number of nuclei with centers (or of which any single point) present in a section of the same thickness plus an additional thickness equal to the average nuclear diameter. Hence, if we count n nuclei with an average diameter of d in a section of thickness t and area 1.6 sq. mm., the number in 1 c.mm. of tissue would be $N = \frac{6n \times 1{,}000}{t + d}$. The number of cubic millimeters in the entire liver has already been calculated as the "assumed total volume," and so the number of cells in the liver can be estimated.

The diameters of forty nuclei were measured with a calibrated micrometer ocular in the area which had been counted. Nuclei were found to be much more variable in size, and on the average larger, in regenerating livers.

A typical calculation follows:

Rat 161. Autopsy Specimen	
Wet weight of whole liver	4.144 Gm.
Wet weight of specimen fixed	2.563 Gm.
Weight of specimen before embedding	2.068 Gm.
Weight of same specimen in oil	0.441 Gm.
Specific gravity of oil	0.856
Volume of specimen (formula 1)	1.900 cc.
Assumed total volume	3.064 cc.
t = 6 microns, d = 7.5 microns, n = 307	
Number of nuclei in 1 c.mm. (formula 2)	137×10^6
Number of nuclei in entire liver	418×10^6

It will be observed that in the foregoing calculation we are estimating the number of hepatic cell nuclei present in an animal's liver. The number of hepatic cells present would be somewhat smaller, depending on how many cells had more than one nucleus. Fishback,[5] Ponfick[6] and Schultz, Hall and Baker[19] have all observed increased numbers of binucleate cells in hypertrophying liver. It was impracticable to try to determine the number of cells present in our section. As a matter of fact, the number of discrete cells in the organ is probably not as absolute as might be supposed. Mann[20] stated that, in general, when an animal fasts the liver cells merge, as the outlines becomes indistinct. Arapow[21] observed that after ingestion of certain foods the livers of white mice showed many more binuclear hepatic cells than otherwise.

Estimation of Size of Liver.—There is one quantity which is of greatest importance in determining the rate of regeneration, a quantity which cannot be measured by our technic directly or indeed by any direct method. That is the

19. Schultz, E. W.; Hall, E. M., and Baker, H. V.: J. M. Research **44**:207, 1923.

20. Mann, F. C., in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 1, p. 231.

21. Arapow, A. B.: Arch. di sc. biol. **8**:184, 1901.

weight of the residual lobes of the liver, the ones not removed at operation, which grow to form the new liver. This quantity added to the weight of the lobes removed would tell the original weight of the liver before partial hepatectomy. It would be better, clearly, to express the amount of regeneration in terms of the amount of the original liver restored, and in order to do this the weight of the original liver must be estimated.

Higgins and Anderson [1] accomplished this by means of a careful statistical analysis of the relationship of liver weight to body weight in their colony of rats. They derived an empirical formula which gives liver weight in terms of body weight in exsanguinated rats. The standard deviation of their relationship is, however, very large; even in a series of ten animals the deviation will be nearly 200 mg. In one of the body weight groups from their chart liver weight varies from about 5.6 to about 8.2 Gm. This method is well suited to the analysis of large groups en bloc. Because of the nature of our problem, however, it was desirable to find a more accurate measure of the size of the residual lobes left in the animal after operation.

TABLE 1.—*Quantitative Relationships Between Main Lobe of Liver, Posterior Lobes and Body Weight*

	Weight, Gm.				Ratio, Percentage		
Rat	Body	Main Lobe of Liver	Posterior Lobes	Total Liver	Liver / Body Weight	Posterior Lobes / Total Liver	Total Liver / Main Lobe of Liver
1	233	4.43	2.20	6.63	2.85	0.332	1.496
2	222	3.39	1.56	4.95	2.23	0.315	1.460
3	167	3.18	1.56	4.74	2.84	0.330	1.491
4	133	3.45	1.51	4.96	3.73	0.304	1.437
5	173	3.90	1.56	5.46	3.16	0.286	1.400
6	158	3.48	1.49	4.97	3.15	0.300	1.434
7	133	2.52	1.27	3.79	2.85	0.335	1.504
8	181	3.49	1.59	5.08	2.81	0.313	1.456
9	162	3.84	1.73	5.57	3.44	0.311	1.451
10	151	3.03	1.49	4.52	2.99	0.330	1.491
11	142	3.41	1.51	4.92	3.47	0.306	1.443
12	133	3.53	1.59	5.12	3.82	0.311	1.451
13	146	3.74	1.90	5.64	3.84	0.336	1.508
Mean	164.2			5.10	3.17	0.316	1.46
Standard deviation σ					0.46	0.015	
Coefficient of variation $\frac{\sigma}{m}$					0.14	0.05	

A series of thirteen rats of the same strain as those used for the later experiments were operated on in the usual way except that the portal vein was ligated posteriorly to the entire liver, and after removal of the main part of the liver the posterior lobe was at once removed. The two fractions of the liver, both exsanguinated in the usual fashion, were weighed separately. A summary of the results is given in table 1.

This table shows that the mean body weight of these rats was 164.2 Gm. and that the mean liver weight was 5.10 Gm. This shows that the livers of our rats were much smaller than the livers of the rats studied by Higgins and Anderson, since according to their formula the mean liver weight in our series should

have been 6.04 ± 0.05 Gm. Aside from the possibility of a genetic difference, it must be remembered that our animals fasted strictly for twenty-four hours before operation, and that the livers were exsanguinated as completely as possible at operation as well as at autopsy.

The ratio between residual liver and total liver in our series was 31.6 per cent ± 1.5 per cent. The coefficient of variation (ratio of standard deviation to average value) of the ratio of residual liver to total liver was 0.05; that of the ratio of liver weight to body weight was 0.14. This indicates that the former relationship is several times as consistent as the latter.

As a final quantitative trial of the validity of estimating liver weight from the known weight of the main part of the liver, a table was made up from our data in table 1 to test the hypothetic case in which each posterior lobe might have grown to 70 per cent of the original liver weight. It was found that when this was calculated from the body weight, the standard deviation was 5.3 per cent; when it was calculated from the weight of the main lobe of the liver, the standard deviation was 1.6 per cent. The last figure, then, indicates the magnitude of the error involved in assuming that the posterior lobe is 31.6 per cent of the total liver, or that the weight of the total liver is 1.46 times the weight of the main lobe of the liver.

We therefore have multiplied the weight of each main lobe of the liver (and likewise the volume and the cell count) by 1.46 and have assumed that this product is the weight of the liver before operation. The standard deviation of this figure is ± 0.03.

An examination of the results for specimens of twenty-eight livers exsanguinated from fasting rats was made to see if there was any greater constancy of the ratio between cell number and body weight than of the ratio between liver weight and body weight. No such constancy was apparent. There were on the average 432×10^6 hepatic cell nuclei per hundred grams of body weight, and in three fourths of the cases this figure was between 362×10^6 and 488×10^6.

The average number of hepatic cell nuclei per gram of wet liver tissue was 143×10^6, and in three fourths of the cases this figure was between 118×10^6 and 161×10^6. The ratio between liver weight and body weight in this same series of animals in percentage was 2.13, and in three fourths of the cases it was between 1.74 and 2.52. No attempt was made to calculate the standard deviations, but it seems obvious that the variability of these three ratios is very much the same. We conclude that for animals of a given weight there is no more constancy in hepatic cell number than in liver weight.

OUTLINE OF EXPERIMENTS

Forty animals were given a bread and milk diet except for the twenty-four hour periods of fasting before operation and autopsy and were killed and examined at various intervals from one to twelve days after removal of the main lobe of the liver. These formed the largest experimental group and served as controls to the other groups.

Six animals were given a diet only of carbohydrate for a week before operation and from then until autopsy (again exclusive of the fasting periods). They received this diet in the form of 10 per cent dextrose solution in unlimited quantity.

Eleven animals received a high protein diet consisting of 75 per cent casein (by weight), 10 per cent cod liver oil, 5 per cent salt mixture and

10 per cent brewers' yeast. This diet contained approximately 70 per cent protein and 4 per cent carbohydrate. It was given ad libitum for a week before operation and afterward.

Thirteen animals received a high fat diet. This was administered as heavy cream, 8 or 10 cc. daily.

A series of seven animals were deprived of food for three and four days, in addition to the preoperative period of fasting, and then were killed in the usual fashion.

Experiments now in progress (report to be published later) are intended to test the influence of certain other factors of growth and metabolism on the rate of growth of regenerating liver tissue.

OBSERVATIONS

Regeneration on a Normal Diet.—As we have demonstrated, the average weight of the posterior lobes remaining in our animals after

TABLE 2.—*Size of Liver Remnant and Number of Cells at Various Postoperative Intervals*

Interval, Days	Volume of Residual Liver*	Volume of Residual Liver Corrected for Loss or Gain of Body Weight	Number of Cells in Residual Liver†
0	31.6	31.6	31.6
1	49.7	54.6	33.5
2	70.1	75.9	52.0
3	79.1	81.9	65.5
4	81.2	83.0	72.0
6	78.9	85.0	81.0
9	94.0	94.5	84.7
12	94.4	85.5	89.0

* Expressed as percentage of the volume of the entire liver before partial hepatectomy.
† Expressed as percentage of the number of cells in the entire liver before partial hepatectomy.

partial hepatectomy expressed as percentage of the original weight of the entire liver is 31.6 per cent. We shall express the growth process in the same terms; that is, we shall record the percentage of the estimated original weight of the liver attained by the remaining liver at various intervals following partial hepatectomy. Table 2 shows this percentage at various intervals of time. The interval in each case is an exact multiple of twenty-four hours.

It will be seen that the remnant does not increase in size significantly between the third and sixth days, and then increases markedly between the sixth and ninth days. The latter interval is, of course, the period during which most of the animals begin to regain the weight which they have lost following laparotomy.

In table 2 is also shown the same ratio corrected for loss or gain of weight of the animals. It shows the relationship between the ratio of residual liver weight to body weight and the ratio of estimated origi-

nal weight of liver to body weight. It will be observed in this case that the curve representing gain in liver size is much smoother. It seems as if the superadded stimulus to liver growth at about a week after partial hepatectomy is conditioned in part at least by the fact that the animals are gaining body weight rapidly during this period. In point of fact, our animals gained 7.8 per cent in weight between the sixth and ninth days and 13.3 per cent between the sixth and twelfth days. Whether this increase in mass is associated with a proportional increase in cell number or not was also investigated.

Increase in Cell Number.—If we turn to the figures expressing the increase in cell number (table 2), we find that during the first twenty-four hours, when rapid increase in size of the liver fragment has been taking place, practically no increase in the number of cells has occurred. From that time on, the number of cells increases rapidly. These values are shown graphically in chart 1, along with the data on increase in

TABLE 3.—*Liver Regeneration During Starvation*

Interval, Days	Weight of Residual Liver*		Weight of Residual Liver Corrected for Loss of Body Weight		Number of Cells in Residual Liver†	
	Starved Rats	Fed Rats (Controls)	Starved Rats	Fed Rats (Controls)	Starved Rats	Fed Rats (Controls)
0	31.6	....	31.6	....	31.6	....
1	49.7	....	54.6	....	33.5	....
2	....	70.1	....	75.9	....	52.0
3	55.0	79.1	64.2	81.0	66.1	65.5
4	52.7	81.2	64.7	83.0	71.6	72.0

* Expressed as percentage of the weight of the entire liver before partial hepatectomy.
† Expressed as percentage of the number of cells in the entire liver before partial hepatectomy.

weight from table 2. It will be noted that growth in cell number lags behind growth in mass throughout.

Effect of Starvation.—A series of seven animals were allowed no food at all from the time of initial fasting twenty-four hours before operation until autopsy three or four days after operation, being given only water. We have included in this series our previous figures for the one day interval, since in that series the two fasting periods were continuous. The results are given in table 3.

It will be noted here that, although the liver weight practically does not increase after the first day, the number of cells increases almost as rapidly as in the animals which have been fed. The body weight lost in the four fasting animals at the end of the three day interval was 14.1 per cent, while in the fed controls it was 7.8 per cent; in the three fasting animals at the end of the four day interval it was 20.2 per cent and in the controls 2.8 per cent.

Chart 2 shows the results of table 3 graphically. In every individual instance, as well as in the averages, animals deprived of food three and

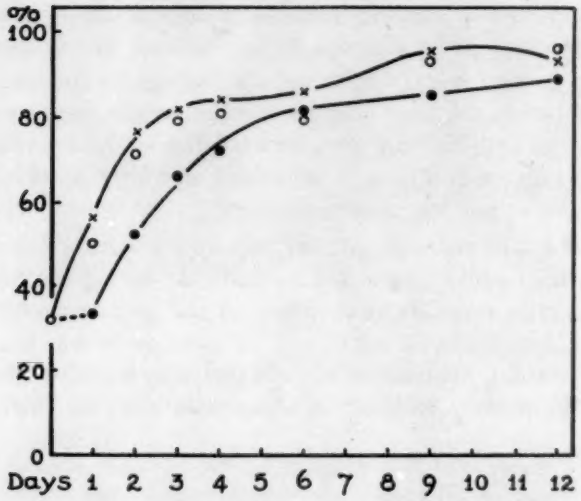

Chart 1.—The upper curve represents growth in liver mass corrected for changes in body weight (liver growth expressed as percentage of original weight regained). The lower curve represents growth in cell number (expressed as percentage of original cell number regained). The circles represent growth in mass not corrected for changes in body weight.

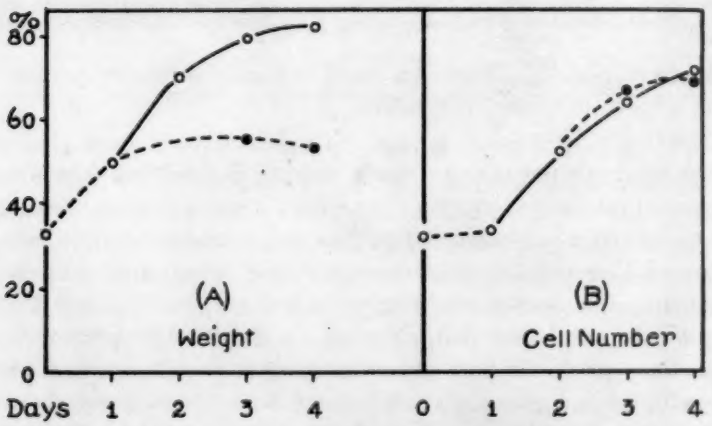

Chart 2.—(*A*) Liver growth in mass (expressed as percentage of original weight regained); (*B*) liver growth in cell number (expressed as percentage of original cell number regained). The broken line represents starved animals; the solid line, fed animals.

four days showed greater percental cell restoration than tissue restoration. The opposite was true of fed animals.

Effect of Diet.—Table 4 shows the results of observations on animals fed diets high, respectively, in carbohydrate, protein and fat for two, three and four day periods after operation and for several days before operation. All diets were well taken. It is obvious that growth of liver in mass is less on a diet of carbohydrate or of protein than on one of bread and milk but greater than on no food at all. Growth in cell number is within normal limits or perhaps slightly retarded on these diets. Growth in cell number appears to be much decreased in animals fed on heavy cream; it is significantly less than in animals on any other diet and much less than in starved animals.

TABLE 4.—*Effect of Diet on Liver Regeneration*

Days	Number of Animals	Series	Weight of Residual Liver*	Weight of Residual Liver Corrected for Change in Body Weight	Number of Cells in Residual Liver†
2	5	Control	70.1	75.9	52.0
2	2	Carbohydrate	54.8	58.6	51.8
2	3	Protein	56.8	62.3	52.2
2	2	Fat	54.2	58.2	37.2
3	7	Control	79.1	81.0	65.5
3	2	Carbohydrate	63.7	68.9	57.0
3	2	Protein	60.9	67.1	51.8
3	3	Fat	70.6	77.8	47.9
3	4	Starved	55.0	64.2	66.1
4	4	Control	81.5	83.0	72.0
4	2	Carbohydrate	68.6	76.2	69.2
4	2	Protein	68.1	74.0	61.7
4	2	Fat	91.7	108.6	51.0
4	3	Starved	52.7	64.7	71.6
6	4	Control	78.9	85.0	81.0
6	2	Fat	86.3	98.5	59.1
9	4	Control	94.0	94.5	84.7
9	2	Fat	109.5	121.4	71.4

* Expressed as percentage of the weight of the entire liver before partial hepatectomy.
† Expressed as percentage of the number of cells in the entire liver before partial hepatectomy.

Nitrogen Content of the Liver During Restorative Growth.—In most cases, as noted before, a portion of the liver removed at operation and a portion removed at autopsy were weighed and placed in concentrated sulfuric acid, following which the total nitrogen was estimated by the macro-Kjeldahl method. Such determinations were made in duplicate and the percental value of nitrogen in the tissue calculated.

The mean percental value of nitrogen in the livers of thirty-six animals on a normal diet, which were analyzed after removal at operation, was 3.51 ± 0.26. Table 5 shows the mean percental value of nitrogen found in livers of animals on normal diets at stated intervals following operation, and the ratio of this to the percental value of nitrogen in the liver tissue taken from the same animals at operation.

It is clear that the material added during the first day or two contains less nitrogen than at later times. The data suggest that the nitrogen content of regenerating liver is still below normal well into the second week of growth.

Calculating from the data, we find that the main lobes of the livers removed from the five one-day animals weighed in all 15.23 Gm. The residual lobes would, therefore, have weighed about 7 Gm. and must have added about 4.05 Gm. of tissue in the twenty-four hour interval, since these lobes at the end of that time weighed 11.05 Gm. The amount of nitrogen in the residual lobes increased in the same period from 0.233 to 0.295 Gm. The 4.05 Gm. of tissue added contained 0.62 Gm. of nitrogen, or 1.39 per cent.

The nitrogen content of tissue added between twenty-four and forty-eight hours, calculated in a similar way, was about 3 per cent.

TABLE 5.—*Nitrogen in Regenerating Liver in Rats on Normal Diet*

Interval, Days	Nitrogen, per Cent	Ratio to Original Nitrogen, per Cent	Number in Series
0	3.51	.....	36
1	2.67	0.805	5
2	2.83	0.818	4
3	3.13	0.929	6
4	3.18	0.891	5
6	3.63	0.951	4
9	3.27	0.908	5
12	3.31	0.944	4

COMMENT

A striking outcome of this investigation is the fact that, although the remnant of liver increases in size between 50 and 60 per cent during the first twenty-four hours after operation, there is no significant increase in the number of hepatic cells. This is consistent with the general impression that mitotic division is not noticeable during the first hours of restoration. Since there is no microscopic evidence of disproportionate increase of other elements of the liver or of intercellular fluids during this period, it is likely that the hepatic cells have increased in size by approximately a similar amount. During the second day, the weight increases 44 per cent and the number of cells 64 per cent. During the third day, the increase in weight is less than 10 per cent, and that in cell count is about 26 per cent. The mean size of the cells decreases, therefore, after cell division sets in; but during the entire twelve days of our observation the mean size of the cells remains a little greater than in resting liver.

Much evidence has been adduced in recent years to show that the important stimulus to growth in restoration of the liver is the portal

blood flow, which after partial hepatectomy is all diverted to pass through a very small remnant of the liver. Even if the primary stimulus to growth should be some physiologic insufficiency, it seems justifiable to consider that this stimulus is applied at the time of or shortly after operation, inasmuch as the increase in mass of liver is so great during the first day. It is interesting consequently that cell division follows only after a latent period of about twenty-four hours, and lags, throughout, behind the increase in size. It is uncertain what the intermediary conditions are between increase in size and the onset of cell division several hours later.

It might appear that mitosis follows as a result of expansion of the size of individual cells. In the case of starved animals, on the other hand, although the liver hypertrophies during the first day, it remains about the same size from twenty-four hours on. Nevertheless, increase in cell number continues through the third day at the same rate as it does in animals which have been fed. By this time, in each animal in our series, the cells are smaller than those in resting liver, even making a reasonable allowance for possible decrease in intercellular fluid, yet they continue to divide.

It would be very interesting to know what the exact nature of the material added during the first day is. We have shown that the additional tissue contains less than half as much nitrogen as resting liver tissue. Higgins and Anderson [1] have shown that its water content is similarly much less than that of normal liver. It seems likely that much of the incremental material may be fat, since a great deal of fat is seen in sections of liver removed after twenty-four hours, and since a considerable amount of fat could be added without necessitating a great increase in the water content. It seems impossible, from our analyses for nitrogen, that much protein can enter into the first day's increment.

If we cause the liver to take up large quantities of fat by means of a high fat diet, we find that the normal rate of cell increase is inhibited. It is apparently not a deficiency effect, since this inhibition is not seen in starvation or on other restricted diets. It appears to be a toxic result of fat feeding. It is noteworthy that, although the fat content of resting liver on a high fat diet is markedly increased (on the basis of microscopic examination), the fat content of these livers while regenerating is still much greater.

Our observations on fat-fed animals are in accord with those of Davis and Whipple [15] on the effect of a high fat diet on restoration of liver cells after the destruction following ether poisoning. We have noticed only slight decreases in the rate of cellular multiplication on various other diets and no difference at all in starvation.

We have noted the same secondary acceleration of liver mass after the first week that was described by Higgins and Anderson.[1] This secondary increase does not appear in the cell number, however. This fact suggests that it may not be a fundamental phenomenon of the growth process. We have hinted that it may be in part due to the fact that at that point the animals are beginning to regain weight lost as a result of laparotomy. We have seen that after correcting the figures so as to make the expected total liver weight at all times proportional to the body weight, the secondary acceleration of growth is less marked. Bearing in mind the observation of McLennan and Jackson,[22] who showed that in chronic inanition the liver weight decreases out of all proportion to the body weight (they observed, in point of fact, that while the body weight decreased 34 per cent, the liver weight decreased 58 per cent), it seems possible that this phenomenon may be entirely due to the fact that the rats are regaining appetite and body weight. It may be, in other words, that during the first week the liver is regenerating toward the size of the liver of an underfed animal, and during the second week, toward that of an animal in better condition. As in the case of our starved animals, cellular increase goes on at an equal rate regardless of nutrition.

Aside from the secondary increase in the second week, our curve of restoration of liver size follows the course of a process which begins at a maximal rate and is progressively retarded as the final size is reached. The curve of cellular restoration shows little or no rise for the first day and from then on follows a similar course. Whether the first increase in cell number begins suddenly or gradually, our data fail to indicate.

SUMMARY AND CONCLUSIONS

A series of rats were subjected to partial hepatectomy, about 70 per cent of the liver being removed. Examination of the residual liver tissue was made at intervals up to twelve days. Estimates were made of the increase in liver mass at various times. By a technic which is described, it has been possible to determine also the increase in cell number.

The number of hepatic cells in the resting livers of our rats ranged from 350 times 10^6 to 500 times 10^6 per hundred grams of body weight. For animals of a given weight there is no more constancy in hepatic cell number than in liver weight.

The mass of the residual liver fragment increases over 50 per cent in the first twenty-four hours after operation and over 100 per cent in the first forty-eight hours. A secondary acceleration of this growth

22. McLennan, C E., and Jackson, C. M.: Arch. Path. **15**:636, 1933.

occurs after six days, but this may be incidental to the fact that at this time the animals begin to regain weight lost postoperatively.

The number of cells in the residual fragment shows no significant increase in the first twenty-four hours. After the first day, it increases at about the same rate as the mass increases initially. There is no secondary acceleration of this increase after the first few days.

In animals starved following operation, the liver mass increases much less than in fed animals, but the number of cells increases at approximately the same rate as in fed animals.

On high carbohydrate and high protein diets, the mass of the liver increases less than on a normal diet, but the increase in cell number is not so much affected. On a high fat diet, the cell increase is markedly cut down, much more so than in starvation.

The normal nitrogen content of fasting rat livers in our series is 3.5 per cent. The tissue which is added during the first day contains 1.4 per cent nitrogen. From that time on, the restored liver rapidly approaches normal liver in nitrogen content.

The rate of restoration of liver tissue is markedly affected by diet. The rate of restoration of cells appears in general to be less dependent on diet and on the growth in mass of the tissue.

General Review

DIFFUSELY INFILTRATIVE CARCINOMA

A HITHERTO UNDESCRIBED CORRELATION OF SEVERAL VARIETIES OF TUMOR METASTASIS

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The curious lesion known as lymphangitic carcinomatosis of the lungs has been on record for almost a century. It has usually formed the subject of individual articles or monographs in which the lesion has been considered either by itself or only in relation to the coexisting primary carcinoma.

The present study attempts a wider scope and aims to show that lymphangitic carcinomatosis of the lungs is merely the pulmonic manifestation of a distinctive variety of carcinoma metastasis which also tends to produce characteristic hematologic changes through involvement of the bone marrow and which in occasional cases has also been associated with diffuse carcinomatous infiltration of the ovary, producing therein the so-called Krukenberg tumor.

For this general type of lesion the name "diffusely infiltrating carcinoma" is proposed.

In order to demonstrate the anatomic unity of the apparently diverse metastatic lesions aforementioned it is necessary to examine case reports, published and unpublished. The case reports in the literature are frequently presented from one particular point of view and tend to slight or to omit incidental data which are apparently of no significance at the time of publication. Thus it is found that most case reports of lymphangitic carcinomatosis of the lungs lack descriptions of the bone marrow. Frequently the blood counts are unreported. Thus there are unavoidable lacunae in the evidence, especially in the older literature. The total number of cases collected, however, is so great that these deficiencies are largely supplied.

The term "lymphangitic carcinoma" is a misnomer, since it suggests the presence of lymphangitis. The term "lymphatic carcinoma," used by Wu,[1] tends to suggest that the tumor is of lymphoid character. It has therefore appeared advisable to conform to the custom which

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1. Wu, T. T.: J. Path. & Bact. **43**:61, 1936.

has prevailed for many years and retain the term "lymphangitic carcinoma" despite its obvious inaccuracy.

The term "diffusely infiltrating carcinoma" is based on a suggestion by Seemann and Krasnopolski.[2]

CLINICAL AND ANATOMIC PICTURE OF LYMPHANGITIC CARCINOMATOSIS OF THE LUNGS

In 1858 Demme[3] reported a series of seven cases of a condition characterized by marked respiratory symptoms such as tachypnea, dyspnea and unproductive cough in the absence of hemoptysis and distinctive physical signs. The pulse rates ranged as high as from 120 to 135. The patients weakened rapidly, showed anemia, anorexia, diaphoresis, cerebral symptoms and often edema, and died. Although little fever was present,[4] such diagnoses as typhoid fever and acute tuberculosis were entertained. Autopsy showed widely disseminated tiny nodules in the pleura and lung in all cases, often with similar involvement of other viscera. To this condition the name "carcinosis miliaris acuta" was given.

Three years after the work of Demme two case reports were published by Erichsen[5] under the title "Carcinosis Acuta Miliaris." One of these concerned a woman aged 47 with carcinoma of the breast who had the rapidly increasing dyspnea and tachypnea which were later to be recognized as typical. The lungs were found to be filled with minute nodules of tumor.

Wagner[6] in 1863 devoted a special study to cancer of the pulmonary and pleural lymphatics. A fine reticular tracery of congested pleural lymphatics was described, from which minute amounts of comedo-like material could be expressed. In two instances the stomach showed diffuse thickening and induration. Unhappily both clinical and microscopic data are scant in this report.

The publications of Troisier[7] provided the really fundamental description of the lesion in the lung and pleura and are referred to by most subsequent students.[8] It was apparently Troisier who introduced

2. Seemann, G., and Krasnopolski, A.: Virchows Arch. f. path. Anat. **262**: 697, 1926.

3. Demme, H.: Schweiz. Monatschr. f. prakt. Med. **3**:161, 1858.

4. Temperatures were measured in four of the seven cases. It will be remembered that clinical thermometry was not in general use at this time.

5. Erichsen, J.: Virchows Arch. f. path. Anat. **21**:465, 1861.

6. Wagner, E.: Arch. d. Heilk. **4**:538, 1863.

7. Troisier, E.: Bull. Soc. anat. de Paris **48**:834, 1873; Arch. de physiol. norm. et path. **1**:354, 1874. Troisier, E., and Letulle, M.: Arch. de méd. expér. et d'anat. path. **13**:243, 1901.

8. See also Raynaud, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **11**:66, 1874. Hillairet, M.: ibid. **11**:78, 1874.

the term "carcinomatous lymphangitis," which has been used especially in the French and Italian literature. It may be said that the subject in general is more extensively treated in the French literature than in any other, and that it has been virtually ignored by American and English authors.

The case reported by Beger [9] is one of the earliest of the cases which come near being clinically typical:

A woman aged 20 had had severe abdominal pain for a month. She was found to have pallor and epigastric tenderness. The heart and lungs were normal to physical examination. The pulse was 132; the respiratory rate, 28. There was slight cough. The respiratory symptoms came to overshadow the gastric symptoms as the respirations increased to 36, then to 48, and very severe cyanosis and dyspnea supervened. Autopsy disclosed carcinoma of the stomach and of the adjacent lymph nodes and extensive lymphangitic metastases in the lungs. In view of certain facts to be discussed in later paragraphs it is interesting to observe that the patient also had carcinomatous infiltration of the pelvic wall.

With the publications of Bard,[10] Girode,[11] Le Noir and Courcoux,[12] Giroux,[13] Bernard and Cain,[14] Collin [15] and Bouchut and Contamin [16] the anatomic and clinical features of lymphangitic carcinosis of the lung were firmly established and correlated. The contribution of Bard [10b] requires to be reviewed in detail:

There were two patients. One, a man aged only 32 years, had pyrosis, diarrhea and emaciation. He was extremely and increasingly dyspneic, yet examination of the chest revealed only a few râles. The temperature remained below 100 F. Autopsy showed carcinoma of the greater curvature of the stomach. The voluminous lungs weighed 1,550 and 1,250 Gm., respectively, and had the lesions of the lymphangitic type of carcinomatous metastasis. The other patient was but 30 years old. He had had violent dyspnea for two weeks, also hematemesis and melena. Despite the menacing respiratory symptoms, auscultation of the chest revealed no abnormalities. Autopsy showed an ulcerated carcinoma of the lesser curvature of the stomach with extensive metastases in abdominal lymph nodes. The pulmonary lesions in this case are so clearly and beautifully described as to deserve quotation: "Dans la plevre il existe surtout à la base une injection blanchâtre de tous les vaisseaux lymphatiques. Sur les poumons, l'absence de noyaux métastatiques et par contre la généralisation des lymphangites se presente sur les coupes sous l'aspect d'un semis de grains de semoule donnant l'impression d'une granulie très fine." (In the pleura there is, especially at the base, a white

9. Beger, A.: Deutsches Arch. f. klin. Med. **23**:357, 1879.

10. Bard, L.: (*a*) Lyon méd. **47**:239, 1884; (*b*) Semaine méd. **26**:145, 1906; (*c*) Rev. méd. de la Suisse Rom. **38**:5, 1918.

11. Girode: Arch. gén. de méd. **1**:50, 1889.

12. Le Noir and Courcoux: Presse méd. **16**:757, 1908.

13. Giroux: Presse méd. **16**:71, 1908.

14. Bernard, L., and Cain, A.: Arch. de méd. expér. et d'anat. path. **25**:333, 1913.

15. Collin, M.: Presse méd. **29**:20, 1921.

16. Bouchut, L., and Contamin: Presse méd. **29**:509, 1921.

injection of all the lymphatic vessels. In the lungs the absence of metastatic nodes and, on the other hand, the generalization of lymphangitis are represented in the sections under the aspect of a mass of grains of tapioca, giving the impression of a very fine miliary state.)

Bard in Gallic fashion distinguished three types of carcinomatous lymphangitis. In the first the lesions are so fine as to be invisible in the gross. In the second type the lesions are visible and may be confounded with small miliary tubercles or lymphangitis. In the third type there is a network of congested lymphatics with small nodular formations at points of intersection. The clinical phenomena are well summarized as follows:

"The progressive rapid development of intense dyspnea without sufficient auscultatory explanation in a patient with hematemesis or other positive sign of a cancerous or ulcerative lesion in the stomach must always make one think of it [lymphangitic metastasis in the lungs]. . . . The possibility must be considered even in patients in whom the diagnosis of a primary cancer cannot be made, since it often happens—especially in the young—that this cancer produces larval symptoms easily misunderstood."

The report by Girode [11] describes a clinically typical case:

A woman aged 30 had malaise, weakness, anorexia and postprandial pain for a month. The chest was very slightly dull to percussion. The epigastrium contained a palpable mass. The respiratory rate increased from 30 to 46 and then to 50. There were a slight dry cough and an occasional basilar râle. Marked cyanosis supervened, and the patient died with signs of asphyxia. Autopsy disclosed a flat infiltrating carcinoma of the stomach. There was typical lymphangitic carcinomatosis of the lungs. The description is accurate and perspicuous but too long to be quoted. It is important to note that the total duration of symptoms was only four months.

In the case reported by Krokiewicz [17] symptoms lasted only forty days.

The patient, quite characteristically, was aged 22 years, and had dyspnea, low fever, slight cough and pains in the bones. The chest was resonant. The lumbar vertebrae were tender but were roentgenologically normal. Roentgen films of the chest showed streaky lines in the lung fields. Cyanosis supervened, and the respiratory rate reached 42. Autopsy showed a walnut-sized ulcerated pyloric carcinoma with metastases in the bone marrow and lymphangitic carcinomatosis of the lungs.

The case of Turrettini and Gerber [18] exhibited an interesting and possibly significant complication:

A woman aged 30 had an infiltrating carcinoma of the stomach which was indurated from the cardia nearly to the pylorus. There was lymphangitic carcinomatosis of the lungs with thrombosis of the superior vena cava, right internal jugular vein and right axillary vein.

17. Krokiewicz, A.: Wien. klin. Wchnschr. **32**:561, 1919.

18. Turrettini, G., and Gerber, I.: Rev. méd. de la Suisse Rom. **40**:177, 1920.

Of von Meyenburg's [19] two cases one was notable because of the advanced age of the patient, namely, 71 years. The primary lesion exhibited was a small and clinically latent prepyloric carcinoma. Microscopic examination of the lung showed lymphangitic carcinoma accompanied by widespread endarteritis obliterans. In the second case the primary gastric lesion had the gross appearance of benign ulcer but the microscopic appearance of carcinoma. Von Meyenburg's concept of the pathogenesis of the pulmonary lesion is the one accepted by most observers. It is thought that the tumor cells pass from the stomach to the perigastric lymph nodes to the tracheal and mediastinal nodes. Involvement of these nodes produces stasis of lymph in the lungs. This is followed by retrograde dissemination from the hilus toward the pleura.

In Hegler's [20] case the primary tumor, a small gastric carcinoma, was asymptomatic.

The three cases briefly reported by Cerkanke [21] were all in young people who had severe dyspnea, slight fever and no abnormal pulmonary signs. All three were found to have primary gastro-intestinal carcinoma and lymphangitic carcinosis of the lungs. In discussing these cases Porges attributed the dyspnea to stiffening of the lung by the carcinomatous infiltration of the alveolar septums.

In Ceelen's [22] case the primary tumor was a deeply infiltrating scirrhus of the stomach, almost unrecognizable in the gross. The small blood vessels of the lung were filled with tumor thrombi in all stages of organization.[23] From the standpoints of both gross pathology and roentgenology it is important that no large nodules of tumor were present.

The report by Dalla Volta and Valenti [24] concerns a woman aged 53 whose illness in the space of sixteen weeks ran a precipitous course characteristic of the disease. An excellent roentgenographic survey is presented.

A case reported by Boccard [25] was complicated by thrombosis of the left basilic and saphenous veins. Boccard used the graphic term "la

19. von Meyenburg, H.: Cor.-Bl. f. Schweiz. Aerzte **49**:1668, 1919.
20. Hegler: Berl. klin. Wchnschr. (pt. 2) **58**:937, 1921.
21. Cerkanke, P.: Klin. Wchnschr. **1**:1027, 1922.
22. Ceelen, W.: Med. Klin. **16**:95, 1920.
23. In this connection see the important discussions on Schmidt, M. B.: Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte (pt. 2) **69**:11, 1897. Zahn, F. W.: Virchows Arch. f. path. Anat. **117**:1, 1889. Winkler, K.: Ergebn. d. allg. Path. u. path. Anat. **23**:22, 1930 (especially p. 232 ff.). Stern, A.: Virchows Arch. f. path. Anat. **241**:219, 1923.
24. Dalla Volta, A., and Valenti, A.: Arch. di pat. e clin. med. **2**:568, 1923.
25. Boccard, A.: La forme asphyxiante aiguë de la carcinose secondaire du poumon, Thèse de Paris, no. 236, 1925.

forme asphyxiante aigue de la carcinose secondaire du poumon" (the acute asphyxiating form of secondary carcinosis of the lung).

The well studied case of Gamberini [26] had the interesting and significant complication of chylous ascites. The carcinomatous stomach was diffusely thickened and indurated in almost its entire extent.

In a case reported by Sisto [27] the primary tumor was a carcinoma of the hepatic flexure of the colon. In a case reported by Docimo [28] the primary lesion was in the uterus. In a case reported by Huguenin and Delarue [29] the primary tumor was in the kidney.

A report by Achard, Bariéty, Desbuquois and Sternfeld [30] emphasizes the frequent clinical latency of the primary gastric carcinoma.

Costedoat and Codvelle [31] reported an unusual case:

A man aged 34 had undergone at the age of 26 gastric resection for carcinoma (*epithelioma métatypique*) and later had tuberculosis with sputum containing tubercle bacilli. Progressive dyspnea and night sweats then developed, but he remained afebrile. X-ray films showed fine linear opacities in the lungs. Autopsy showed linitis plastica in the resected gastric remnant—a scirrhus poor in epithelial elements. The lungs were grossly firm. No nodular or granular lesions could be seen, and there was no pleural network of tumor visible, although small creamy cylinders could be expressed. Microscopically the pulmonary lymphatics were found to be enormously distended with tumor cells.

Interesting reviews of the subject of lymphangitic carcinomatosis of the lung are those of Moretti,[32] Poppi [33] and Greenspan.[34]

Moretti [32] reported a case primary in the ovary and characterized by a respiratory rate of 42. Of particular note is the fact that the patient had frequent epistaxis unaccompanied by other signs of a hemorrhagic tendency.

The case reported by Poppi [33] presented an interesting concatenation of clinical and anatomic occurrences:

A man aged 49 had had flatulence, abdominal oppression and anorexia for a year. This was followed by supraclavicular pain and by edema of the left arm. Examination confirmed the existence of this edema and revealed the presence of chylous ascites and Virchow's node. Despite increasing dyspnea, tachypnea and cyanosis, physical examination of the chest detected only slight dulness and very

26. Gamberini, M.: Policlinico (sez. med.) **35**:493, 1928.
27. Sisto, P.: Minerva med. (pt. 2) **8**:1311, 1928.
28. Docimo, L.: Tumori **3**:601, 1929.
29. Huguenin, R., and Delarue, J.: Ann. d'anat. path. **7**:524, 1930.
30. Achard, C.; Bariéty, M.; Desbuquois, G., and Sternfeld: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:184, 1931.
31. Costedoat and Codvelle, F.: Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1159, 1932.
32. Moretti, E.: Riv. di clin. med. **34**:639, 1933.
33. Poppi, A.: Arch. di pat. e clin. med. **14**:487, 1935.
34. Greenspan, E.: Arch. Int. Med. **54**:625, 1934.

fine râles. X-ray films of the chest showed a widespread fine reticular shadow and scattered submiliary opacities. A clinical diagnosis of gastric carcinoma with glandular and peritoneal metastases and lymphangitic carcinomatosis of the lung was therefore made. This was confirmed at autopsy. Since the left subclavian vein was thrombosed it seems likely—in view of the chylous ascites—that the thoracic duct was also obstructed, presumably by tumor.[35] It is conceivable that obstruction of the thoracic duct produced thrombosis of the left subclavian vein or vice versa.

The excellent paper by Greenspan [34] reports four cases of lymphangitic carcinomatosis of the lungs; three of these cases showed diffuse obliterative endarteritis of many pulmonary arterioles. Greenspan attributed the endarteritis chiefly to intimal hyperplasia due to the presence of tumor cells in the perivascular lymphatics. In two of the cases diffuse obliterative endarteritis of the pulmonary vessels apparently produced failure of the right side of the heart. In one case the diagnosis of lymphangitic carcinomatosis of the lungs was made ante mortem.[36]

A recent paper by Wu [1] reviews forty-nine cases of lymphangitic carcinomatosis of the lungs. Eighteen of the cases occurred in persons under 40 years of age. In thirty-six cases the primary tumor was in the stomach. Eight cases showed obliterative changes in the pulmonary vessels. In five originai cases reported by Wu the condition of the bone marrow is not described.

Summary.—From the foregoing mass of data a clinical and anatomic entity is formed with ease. The patient is often a young adult [37] or one in early middle life.[1] He has a primary carcinoma, usually in the stomach, and most often of the scirrhous type. The gastric symptoms are frequently mild [11] or absent [20] and tend to become overshadowed by respiratory symptoms. The latter consist of rapidly increasing dyspnea, tachypnea, cyanosis and inconspicuous unproductive cough without obvious cause. Physical examination of the thorax often reveals no abnormal signs [21] or may show slight signs [24] such as mild dulness or even hyperresonance, slight harshness of breath sounds and occasional accentuation of the second pulmonic heart sound.[38] The respiratory symptoms are usually severe, accelerative and brief.[15] Fever is usually

35. Patoir, A.; Warembourg, H., and Bédrine: Paris méd. **2**:229, 1934. Menetrier and Piot: Bull. Assoc. franç. p. l'étude du cancer **4**:222, 1911. Yater, W. M.: Ann. Int. Med. **9**:600, 1935. Leydhecker, O.: Virchows Arch. f. path. Anat. **134**:118, 1893. Unger, E.: ibid. **145**:581, 1896. Schwedenberg, T.: ibid. **181**:295, 1905. Winkler, K.: ibid. (supp.) **151**:195, 1898. Cunéo, B.: De l'envahissement du système lymphatique dans le cancer de l'estomac et de ses conséquences chirurgicales, Thèse de Paris, no. 179, 1900.

36. In the case reported by C. Rabin (J. Mt. Sinai Hosp. **2**:246, 1936) no autopsy was performed.

37. Beger [9] cites a case in a girl aged 15 years.

38. Erichsen.[5] Gamberini.[26]

slight or absent. The patient dies with the appearance of asphyxia [39] or with failure of the right side of the heart.[34]

Autopsy reveals the presence of a primary carcinoma, usually in the stomach [40] but occasionally in other viscera.[41] The primary tumor in the stomach is often a scirrhous or flat diffusely infiltrating lesion [42] which may assume the appearance of linitis plastica [43] or may escape recognition in the gross or may be recognizable with difficulty.[44] Abdominal lymph nodes are usually involved.

The lungs may appear normal in the gross, and the presence of tumor in the lungs may accordingly be unsuspected until microscopic preparations are examined.[12] In other cases there is a gray or white network of subpleural lymphatics distended with tumor. Cut surfaces of the lungs show minute granules and fine lines of tumor tissue in lymphatics; these are most prominent about bronchioles and blood vessels. Well marked cases show minute nodules at points of intersection of the lines previously described. Large rounded discrete tumor metastases are not found. Frequently the lungs appear voluminous.[45] Microscopically groups of tumor cells are found in distended perivascular, peribronchial and subpleural lymphatic spaces. Obliterating endarteritis may occur concomitantly.[46] Organizing tumor thrombi may be found in the blood vessels.[22]

The mediastinal lymph nodes have usually been found to contain tumor.

In most of the cases pleural effusion has been absent or the amount too small to be regarded as the cause of the dyspnea which is the outstanding clinical characteristic. Occasional cases have, however, shown pleural effusion associated with signs of heart failure.[34]

Chylous effusions have been found infrequently.[47] Two patients have shown edema of the left arm and other signs highly suggestive of obstruction of the thoracic duct.[48]

In several cases the diagnosis has been made intra vitam and verified at autopsy.[49]

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39. Boccard.[25] Costedoat and Codvelle.[31]
40. Wu.[1] Poppi.[33]
41. Bernard and Cain.[14] Sisto.[27] Docimo.[26] Huguenin and Delarue.[29]
42. Bard.[10a] Girode.[11] Turrettini and Gerber.[18] Gamberini.[26]
43. Le Noir and Courcoux.[12] Costedoat and Codvelle.[31]
44. Terplan, K., and Sommer, G.: Beitr. z. path. Anat. u. z. allg. Path. **87**:228, 1931. Ceelen.[22]
45. Bard.[10b] Girode.[11] Dalla Volta and Valenti.[24]
46. von Meyenburg.[19] Greenspan.[34]
47. Gamberini.[26] Poppi.[33]
48. Boccard.[25] Poppi.[33]
49. Porges, O., in discussion on Ceelen.[22] Bard.[10c] Greenspan.[34] Schmidt and others.[23]

CLINICAL AND ANATOMIC PICTURE OF METASTATIC CARCINOMA OF THE BONE MARROW ASSOCIATED WITH THROMBOPENIA AND PURPURA

Since the time of Hayem [50] it has been held that the platelets are increased in number in cases of carcinoma. Hayem's dictum is copied by Naegeli [51] without further comment. Perl,[52] however, found that the number of platelets is usually at the lower limits of normal. Rosenbaum [53] found them generally increased in number.

It has been known for many years, however, that certain cases of carcinoma are characterized by a hemorrhagic tendency.

Thus Epstein [54] in 1896 reported the case of a woman with scirrhous carcinoma of the left breast who had epistaxes, hematemeses and severe anemia. Autopsy showed extensive metastases in the bone marrow, as well as in other organs. The blood smear contained many immature erythrocytes and leukocytes; unfortunately no blood counts and no platelet counts were made. It is of interest that this patient had a respiratory rate of 48 and had tumor in the pleural lymphatics. No microscopic data are given concerning the lungs.

Frese [55] in 1900 reported two highly interesting cases of carcinoma of this type.

The first patient, a man only 26 years of age, had hemorrhages in the skin, mouth and eyes, with severe secondary anemia and leukocytosis. Normoblasts were found in the circulating blood. After the disease had followed a clinical course of only four weeks, the man died. Autopsy revealed a pyloric carcinoma with extensive submucosal and only slight mucosal involvement. There were extensive metastases in bones. Interestingly enough, the lungs showed lymphangitic carcinomatosis. The second patient was similarly young—28 years old. She had a palpable epigastric mass, pain in the abdomen and extremities, retinal hemorrhages and terminal dyspnea. There was severe secondary anemia; myelocytes and megaloblasts were found in blood smears. Autopsy showed carcinoma of the pylorus and of the neighboring lymph nodes and multiple metastases in bones. Carcinomatous injection was also observed in subpleural lymphatic vessels in the lungs. No platelet counts are reported in either case.

Kurpjuweit [56] and Ellermann [57] reported cases of carcinoma with anemia and hemorrhagic diatheses and skeletal metastases. Kurpjuweit's case showed, in addition, hemosiderosis and myeloid changes in the liver, spleen and lymph nodes and a profusion of immature forms in the circulating blood. In neither case are platelet counts reported, nor are the lungs described. Houston's [58] report of a case of mammary carcinoma and purpura is similarly inadequate in detail.

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50. Hayem, G.: Du sang et ses altérations anatomiques, Paris, G. Masson, 1889.
51. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1931, p. 661.
52. Perl, C.: Ztschr. f. klin. Med. **122**:253, 1932.
53. Rosenbaum, B. N.: Zentralbl. f. Chir. **51**:305, 1924.
54. Epstein, J.: Ztschr. f. klin. Med. **30**:121, 1896.
55. Frese, O.: Deutsches Arch. f. klin Med. **68**:387, 1900.
56. Kurpjuweit, O.: Deutsches Arch. f. klin. Med. **77**:553, 1903.
57. Ellermann, V.: Hospitalstid. **6**:352, 1923.
58. Houston, T.: Brit. M. J. **2**:1257, 1903.

In a case described by Schleip [59] there was a clinically latent small carcinoma of the stomach and almost complete replacement of the bone marrow by metastases. The patient had weakness, vertigo, dyspnea (pleural effusion), bone pains, spinal obstruction and small hemoptyses. There was severe secondary anemia, and many immature cells were found in the blood smears. The platelets are said to have been very few (*sehr spärlich*). The lungs were normal grossly; no microscopic data are given.[60]

Two brief reports by Dünner [61] concern young women who had thrombopenic purpura and severe secondary anemia; in one, many immature erythrocytes were present in the blood. Both showed gastric carcinoma with extensive metastases in the bone marrow. In neither case are the lungs described.

Steinfeld and Shay [62] describe a case of gastric carcinoma with purpura, severe thrombopenia and secondary anemia. Large numbers of immature red and white cells occurred in the blood smears. The stomach grossly appeared to contain a healed ulcer; this was shown microscopically to be a carcinoma. Metastases were not demonstrated in the bone marrow, but apparently only the tibial marrow was examined. The lungs are said to have shown only edema. The case is difficult to evaluate and is summarized here merely for completeness.

Equally difficult to understand is the case of Loeper and de Sèze,[63] who reported an instance of severe purpura in which autopsy showed gastric carcinoma with metastases in the liver. The purpura was attributed to hepatic insufficiency resulting from the tumor metastases. It appears that the case cannot be accepted, since no data concerning the bone marrow and no platelet counts are given. The condition of the lungs is likewise not mentioned.

Weingarten [64] described the case of a woman aged 29 who had pain and tenderness in the bones, cutaneous and visceral hemorrhages, urobilinuria and severe anemia. The platelets numbered 19,000 per cubic millimeter. No normoblasts or myelocytes were found in the blood. Autopsy showed a small flat gastric carcinoma with marked submucosal infiltration. Metastases were very widely disseminated through the vertebral column, although x-ray films had shown no abnormality. No data are given concerning the lungs.

Bucci [65] reported the case of a man aged 33 who had epigastric oppression and loss of weight. The man apparently had no purpura but had profuse epistaxis of thirteen days' duration, also retinal hemorrhages. Severe anemia, mild erythroblastosis and urobilinuria were present; no platelet counts are reported. Although roentgen examination of the stomach yielded negative results, autopsy showed an infiltrating carcinoma of the lesser curvature with extensive metastases in lymph nodes and bone marrow. The condition of the lungs is not specified.

Waugh [66] in a discussion of hemolytic anemia associated with carcinomatosis of the bone marrow reports two cases. The first of these falls outside the scope of the present study since no autopsy was performed. The second case was that

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59. Schleip, K.: Ztschr. f. klin. Med. **59**:261, 1906.

60. It will be remembered that in several cases of lymphangitic carcinomatosis of the lung the lesions were not seen in the gross.[12]

61. Dünner, L.: Berl. klin. Wchnschr. **58**:386 and 1107, 1921.

62. Steinfeld, E., and Shay, H.: M. Clin. North America **13**:923, 1930.

63. Loeper, M., and de Sèze, S.: Progrès méd., 1930, p. 282.

64. Weingarten, R.: Zentralbl. f. inn. Med. (no. 18a) **53**:739, 1932.

65. Bucci, C.: Riv. osp. **21**:325, 1931.

66. Waugh, T. R.: Am. J. M. Sc. **191**:160, 1936.

of a woman with carcinoma of the breast, splenomegaly, hyperbilirubinemia, thrombocytopenic purpura and secondary anemia. Many immature leukocytes and erythrocytes were found in stained blood films. Autopsy showed extensive tumor metastases in the bone marrow. "The neoplastic areas in the bone marrow were extraordinary in that they consisted for the most part of emboli of tumor cells, definitely within vascular channels." Metastases were also found in the lungs; the type of metastasis, however, is not specified. During life slight cyanosis had been present.

Cohen [67] reported a case of thrombopenic purpura in a man aged 60 who had carcinoma of the prostate with metastases in the bone marrow. The right lung contained hematogenous metastases having the structure of "pneumonia carcinomatosa."

Herzog and Roscher [68] described a woman aged 50 who had thrombopenic purpura, secondary anemia, immature red and white cells in the circulating blood and urobilinogenuria. Autopsy showed a large cell malignant tumor, probably epithelial and presumably primary in the liver, with metastases in the liver, bone marrow, lymph nodes and spleen. The lungs interestingly enough appeared normal in the gross; microscopic examination showed fine intravascular tumor thrombi.

The cases which remain to be discussed are in general more fully presented by their authors than most of the cases heretofore considered and hence offer a more satisfactory basis for judgment.

Seemann and Krasnopolski [2] reported in detail the case of a woman aged 38 who had thrombopenic purpura, splenomegaly and severe anemia. Of 15,000 leukocytes per cubic millimeter, premyelocytes constituted 1.5 per cent, myelocytes 5 per cent and metamyelocytes 11.5 per cent. Macrocytes and normoblasts were also present. Autopsy showed diffuse carcinomatous thickening of the wall of the stomach and extensive metastases in the bone marrow. The tumor was highly anaplastic. Interestingly enough the lungs appeared normal in the gross; microscopically they showed lymphangitic metastases. Marked hematopoiesis was found in the liver and spleen. There was extensive carcinomatous involvement of mesenteric lymphatics.

Stillman [69] reported the case of a man aged 45 who had cutaneous and visceral hemorrhages and marked thrombopenia. At autopsy no primary tumor was found, and no bone marrow was obtained. The lungs were of especial interest. The visceral pleurae were studded with grayish white spots, from 3 to 5 mm. in diameter, barely raised above the surface. On section, the lung appeared grayish red throughout, was somewhat firmer than usual, and presented an apparent diffuse increase in fibrous tissue. Microscopic studies, however, showed large masses of tumor cells in lymph sinuses throughout the lung tissue and in those beneath the pleura—evidently the typical picture of lymphangitic carcinomatosis. Roentgen examination of the thorax had shown fuzzy-appearing indefinite shadows throughout both lungs.

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67. Cohen, J.: Nederl. tijdschr. v. geneesk. **73**:5485, 1929.

68. Herzog, F., and Roscher, A.: Virchows Arch. f. path. Anat. **233**:347, 1921 (case 1).

69. Stillman, R. G.: M. Clin. North America **14**:1533, 1931 (case 2). Dr. Stillman was kind enough to send me sections from this case and additional data concerning it.

Features of special interest abound in the case of Terplan and Vaughan:[70]

A woman aged 42 who had become weak, emaciated and cachectic was found to have profound anemia and hepatosplenomegaly. Examination of the blood showed severe hyperchromic anemia with macrocytosis. Erythroblasts numbered 62,000 per cubic millimeter; 17 per cent of the erythrocytes were reticulated. The white blood cell count was 8,700, with the differential count showing percentages as follows: myelocytes 18 and polymorphonuclears 56 (juveniles 14, band forms 27 and filamentous forms 15). The platelets numbered 30,000 per cubic millimeter. The profound anemia with thrombocytopenia accompanied by tremendous regenerative effort in both the erythrocytic and leukocytic series was thought to be diagnostic of a sudden extensive encroachment on active bone marrow, such as one might expect from tumor metastases. At autopsy the stomach appeared distinctly contracted. It showed slightly increased mucoid secretion and rather prominent folds. The mucosa was entirely intact. Grossly, infiltration could not be found at any part of the gastric wall. Sections revealed that the gastric lesion was an adenocarcinoma. The ovaries showed a typical Krukenberg tumor. The liver and spleen presented unusually marked myeloid metaplasia, the histologic appearances being hardly different from those seen in true myeloid leukemia.

Through the courtesy of Dr. Terplan I was able to study the sections of lung. These showed groups of tumor cells in lymphatics beneath the pleura and around blood vessels—the picture of lymphangitic carcinoma.

Lawrence and Mahoney[71] reported the case of a man aged 43 who had gastric symptoms, lumbar pain and purpura. There was hypochromic anemia and mild reticulocytosis. Immature erythrocytes and leukocytes were present; the myelocytes on one occasion attained the proportion of 15 per cent. The number of platelets was markedly diminished. Autopsy revealed an annular prepyloric carcinoma of the stomach with extensive metastases in the viscera, including the lymph nodes. Although the bones had been found normal roentgenologically, they contained extensive deposits of tumor.

Special attention is demanded by the condition of the lungs. These showed no gross evidence of tumor. Microscopically, however, "The most striking feature is the distribution of tumor cells. The lymphatics about the bronchi and vessels, and the capillaries of the alveolar walls, are in most areas filled with tumor cells. Also, the smaller vessels and the lymphatics of the pleura show a similar condition . . . There are no areas in which nodules of tumor have eroded lung tissue."

Stebbins and Carns[72] reported the case of a woman aged 21 who had thrombopenic purpura. At autopsy the stomach was found to contain a small nonindurated depressed and puckered lesion resembling a healed ulcer; microscopically this proved to be a somewhat scirrhous adenocarcinoma. There were extensive metastases in bone marrow and lymph nodes. The lungs appeared pale and voluminous in the gross; microscopic examination revealed lymphangitic

70. Terplan, K., and Vaughan, S. L.: Arch. Path. **18**:924, 1934. Dr. Terplan had the kindness to send me sections from this case.

71. Lawrence, J. S., and Mahoney, E. B.: Am. J. Path. **10**:383, 1934.

72. Stebbins, G. G., and Carns, M. L.: Arch. Path. **20**:247, 1935. Dr. Carns and Dr. Stebbins were kind enough to send me a personal communication regarding this case.

metastasis. The authors stated "An interesting feature of this case was the predilection of the tumor cells for the lymphatics, lymph nodes and venous sinuses. Lymphatic involvement in organs was particularly noted in the ovaries and lungs. Not a metastasis was found in the lungs outside the pulmonary lymphatics, which were widely dilated, especially in the peribronchial regions."

Cosin [73] reported the case of a man aged 25 who had pain in the bones, purpura, epistaxis, intra-ocular and cerebral hemorrhages, adenopathy and marked splenomegaly. X-ray films showed punched-out areas widely distributed through the skeleton. Severe secondary anemia was found; many of the red and white blood cells were immature. Autopsy revealed widespread metastatic tumor in bones and viscera. The lungs showed marked peribronchial thickening; a few firm white nodules were found in the pleura. Microscopic examination showed the tumor cells to be large oat-cell forms thought to be of bronchial origin.

In a case of mammary carcinoma with purpura and urobilinuria, Huguenin, Foulon and Rosenrauch [74] found the lungs macroscopically normal. Microscopic examination revealed numerous intravascular emboli of tumor. The condition of the bone marrow was not reported.

The following case is reported through the kindness of Dr. Paul Klemperer of the Mount Sinai Hospital of New York.

A man about 65 years of age had lost 25 pounds (11.3 Kg.) in the past year. One week prior to observation pain developed in the hypogastrium and suprapubic region, then pain and tenderness in the left sacro-iliac region with radiation to the legs. Shortly thereafter purpura was noticed. Examination revealed purpura, fever, abdominal distention, cyanosis and dyspnea. The hemoglobin was 78 per cent. The blood counts were: red cells, 3,500,000; platelets, 30,000; white cells, 7,600, including 70 per cent polymorphonuclears and 3 per cent myelocytes. The bleeding time was four minutes; the coagulation time, eight minutes. X-ray films of the vertebral column disclosed no changes. At autopsy the lungs appeared firmer and less crepitant than normal. No nodules of tumor were seen in the gross. There was no hydrothorax. Microscopic examination showed numerous small carcinoma emboli in the vessels of the lung and pleura. Many of the lymphatic channels of the lung contained fine clumps of tumor cells. There were tumor metastases in the vertebrae, pelvis and lymph nodes. The primary tumor was a carcinoma of the sigmoid.

The following case, from this department, was reported in brief by Copeland.[75]

A woman aged 54 had become increasingly weak for three years. During the last six weeks general enlargement of the lymph nodes had been observed. For three weeks fever and sweats had occurred. Examination revealed pallor, low fever, slight tachycardia and dyspnea. There was a petechial eruption over the abdomen and trunk. The lymph nodes were generally enlarged; the liver was palpable; the spleen was greatly enlarged. Examination of the chest revealed no abnormality other than harshness of breath sounds. The ankles were edematous. The hemoglobin ranged from 58 to 39 per cent; the red blood cell count, from

73. Cosin, L.: Brit. J. Surg. **23**:110, 1935.

74. Huguenin, R.; Foulon, P., and Rosenrauch, C.: Ann. d'anat. path. **8**:1166, 1931.

75. Copeland, M. M.: Arch. Surg. **23**:581, 1931.

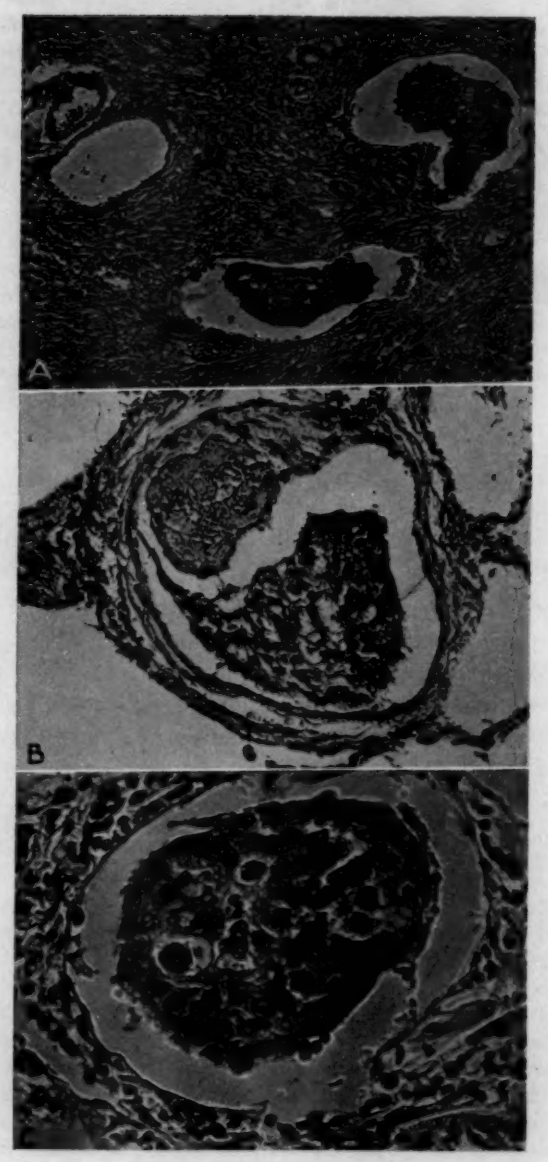

Fig. 1 (case 3).—*A*, groups of tumor cells in lymphatics in the wall of the stomach. *B* and *C*, tumor in lymphatics in the lung.

3,100,000 to 1,900,000. The white blood cell count was 7,400; with polymorphonuclears 30 per cent, myelocytes 26 per cent, myeloblasts 1 per cent, lymphocytes 27 per cent and many normoblasts and megaloblasts. The platelets numbered 340,000 (only one determination made). The urine contained urobilin. Roentgen examination of the chest revealed enlargement of mediastinal lymph nodes. The vertebrae appeared normal roentgenologically. The respiratory rate increased from 28 to 48. At the time of death the diagnosis was chronic myeloid leukemia.

At autopsy the stomach was found to be diffusely thickened and leathery. A huge shallow ulcer extended from the cardia almost to the pylorus and involved almost the entire circumference of the distal half of the stomach. The lungs were moist and showed no grossly visible tumor. The bones were very extensively involved by tumor.

Microscopically the tumor was found to consist of large oblong, oval or rounded cells, loosely arranged and not in the form of tubules or strands but rather as a homogeneous infiltration. There was extensive invasion of lymphatics in the wall of the stomach. In the lung, where no tumor had been recognized grossly, there were long strands and masses of tumor cells in distended lymphatics in the vicinity of vessels and bronchioles and also in the subpleural lymphatics. The spleen was diffusely and almost totally infiltrated by tumor. In the liver every periportal field was obliterated by tumor.

Anatomic Diagnosis: Tumor of the stomach (carcinoma?) with extension to the surrounding tissues and mesentery; metastases in the lymph nodes, spleen, liver, lungs and bones; peritoneal implantations in the pelvis; infiltration about the left adrenal gland.

This case was noteworthy because of the clinical latency of the primary gastric lesion and because of the simulation of leukemia resulting from tumor infiltration of the bone marrow, spleen and lymph nodes. The lung showed the lesions of lymphangitic carcinomatosis, which were probably responsible for the cyanosis and increasing tachypnea. The pulmonary lesions eluded roentgen examination, as did the lesions in the bones.

The following case was also observed in this department:

A colored man aged 23 had had pain in the back for two weeks. For ten days he had had bleeding gums. Examination revealed an ecchymosis on one thigh, sternal tenderness, bleeding gums and palpable liver. There was no adenopathy. The heart and lungs appeared normal. The hemoglobin declined rapidly from 58 per cent to 25 per cent. The blood counts were: red cells, 3,040,000; white cells, 4,500; platelets, 18,000. The bleeding time was fifteen minutes; the clotting time, forty-five minutes; lysis of clot occurred after twenty-four hours. The respiratory rate gradually increased from 20 to 36 per minute. Roentgen examination revealed no lesions in the sternum, ribs, femur and vertebrae.

Autopsy revealed a firm, puckered and slightly ulcerated mass about 5 cm. in diameter, situated on the greater curvature of the stomach. The submucosa was extensively infiltrated. The lungs appeared edematous in the gross; no tumor nodules were seen. The liver appeared smooth and homogeneous and also contained no nodules. The bones were extensively mottled with tumor.

Microscopically the gastric lesion was seen to be a carcinoma composed of abnormal epithelial cells arranged in strands and groups with no tendency to acinar formation. The cells extended in irregular masses and networks through the

submucosa and muscularis. Metastases were far more numerous than had appeared from examination of the gross organs. In the lungs there were masses of tumor in the lymphatics and also in many of the blood vessels, although no tumor could be seen in the gross. In the liver the same condition prevailed; there

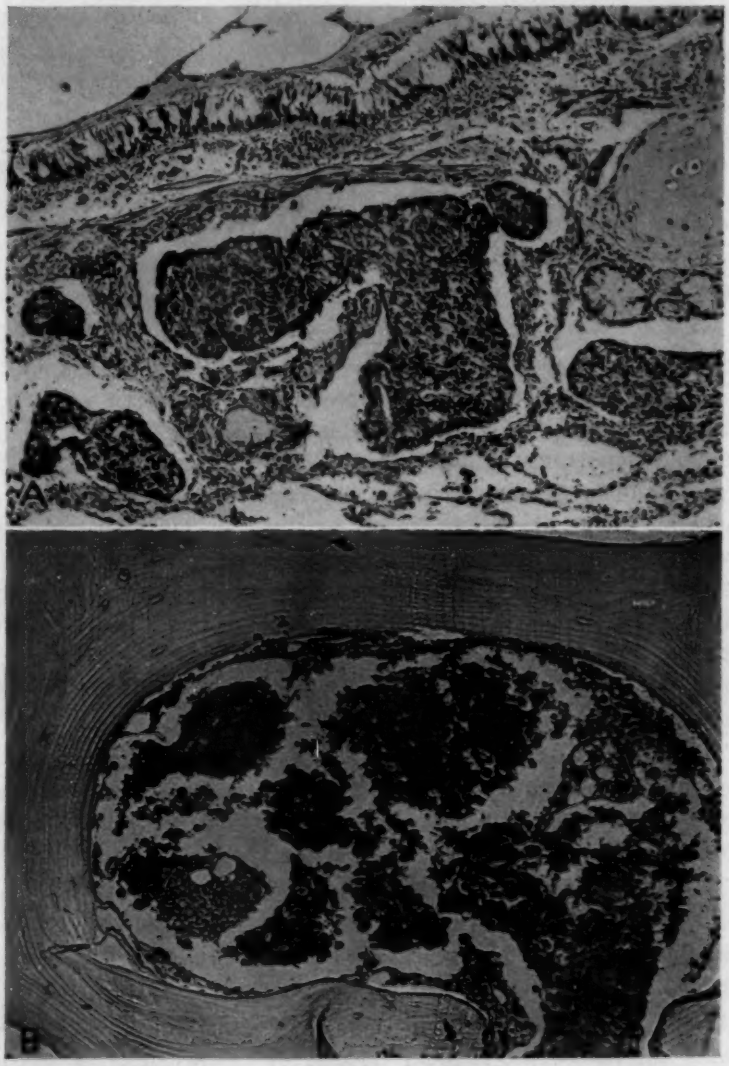

Fig. 2 (case 3).—*A*, tumors in peribronchial lymphatics. *B*, tumor in marrow of intact bone.

were no large nodules, but tumor cells lay in the branches of the portal vein. Large deposits of tumor lay in the marrow spaces of the bones; small areas of marrow survived, but were apparently restricted by extensive newly formed connective tissue.

Anatomic Diagnosis: Carcinoma of the stomach; metastases in the lymph nodes, liver and lung; widespread tumor metastases in the bone marrow, with hemorrhage and necrosis; osteosclerotic anemia; hyperplasia of the femoral marrow; extramedullary blood formation in the liver and spleen, epicardial gastric and subdural hemorrhages.

CORRELATION BETWEEN LYMPHANGITIC CARCINOMA OF THE LUNG, CARCINOMA WITH PURPURA AND KRUKENBERG TUMOR OF THE OVARY

The second part of this study brought together all the cases of carcinoma with purpura which could be found in the literature. To these were added three new cases. Careful scrutiny of the reports of these cases reveals certain facts of compelling interest and significance.

Of the twenty-two patients whose ages are given, one-half were less than 40 years old and one-third were less than 30 years old—a most unusual age distribution for a cancer group.

The primary tumor was in the stomach in fifteen cases, in the breast in three, in the sigmoid in one and in the prostate in one. In three cases the primary growth was not definitely determined. If the fifteen cases of primary gastric carcinoma are segregated and placed in a subgroup, this subgroup will be found to show an age distribution even more unusual than that of the entire series of cases, since two thirds of the cases of gastric carcinoma were in persons less than 40 years of age. Thus it is apparent that the anatomic complex under consideration here tends to occur mainly in young adults who have gastric carcinoma but may occur occasionally in older adults who have carcinoma primary in various organs.

The primary gastric tumors were most frequently scirrhous or diffusely infiltrating growths and often were clinically latent. Often these tumors likewise escaped recognition in the gross at the time of autopsy. Occasionally the primary lesion was of the type called "linitis plastica."

The bone marrow contained extensive deposits of tumor in all cases in which examination was made. The single exception was the case of Steinfeld and Shay,[62] in which only the tibia appears to have been examined.

Equally impressive were the findings in the lungs. There was a striking absence of the familiar nodular or "snowball" type of tumor metastasis. In most of the cases, in fact, no tumor was seen grossly in the lungs. Microscopically almost all of the cases showed lymphangitic carcinomatosis, occasionally associated with fine intravascular groups of tumor cells. In one case report, that of Steinfeld and Shay,[62] tumor in the lungs is not mentioned.

Cases of carcinoma with purpura thus are almost invariably associated with lymphangitic carcinomatosis of the lungs; this may be accompanied by fine intravascular deposits in the lungs.

If the large group of cases of lymphangitic carcinoma of the lungs which formed the first part of this study is reexamined in comparison with the cases of carcinoma and purpura a series of important similarities becomes apparent. Both groups tend to occur predominantly but not exclusively among young adults. In both groups the primary lesion is most often situated in the stomach. In both groups the gastric lesion is most often a scirrhous or diffusely infiltrating tumor and often has been difficult to recognize in the gross. In both groups the gastric lesion has often been unobtrusive or even altogether silent clinically. In both groups the clinical symptoms have usually pursued a brief and accelerative course.

It has been shown in addition that almost all of the thoroughly studied cases of carcinoma with purpura have been characterized by lymphangitic carcinomatosis in the lungs.

The conclusion is therefore inescapable that lymphangitic carcinomatosis of the lungs and carcinomatous deposits in the bone marrow accompanied by thrombocytopenic purpura represent merely two different manifestations of one and the same variety of diffusely infiltrative carcinoma. In any given case of the type under discussion lesions will usually be found in both the lung and the bone marrow, and the clinical picture in any given case will necessarily depend on the predominance of involvement in one site or the other. If the bone marrow is heavily involved the clinical appearances will be those of a blood dyscrasia. If the lungs are heavily involved the respiratory symptoms will attract greatest attention.

Although the hemorrhagic diathesis is perhaps the most conspicuous clinical manifestation of extensive carcinomatosis of the bone marrow, cases are reported in which the hematopoietic disturbance assumed other forms.

Probably the commonest change next to anemia is the occurrence of immature leukocytes and erythrocytes in the circulating blood. This phenomenon was observed almost constantly in the cases with hemorrhage just described but may also occur apart from any hemorrhagic tendency.

Thus Melocchi [76] reported the case of a man aged 61 who had a diffuse type of gastric carcinoma with lymphangitic carcinoma of the lung. There was moderate anemia with a color index varying between 0.9 and 1.6. Megalocytes and megaloblasts were present. No platelet count was reported, and no purpura was observed. The urine contained urobilin.

76. Melocchi, W.: Riforma med. **49**:476, 1933.

The case of Terplan and Vaughan [70] has already been noted. Autopsy disclosed infiltrating carcinoma of the stomach, lymphangitic metastases in the lungs and extensive deposits in the bone marrow. Examination of the blood showed: hemoglobin, 44 per cent; red blood cells, 1,700,000 per cubic millimeter, of which 17 per cent were reticulated; erythroblasts, 62,000; white blood cells, 8,700. The differential count gave percentages as follows: myelocytes, 18, and polymorphonuclears, 56 (juvenile forms, 14; band forms, 27, filament forms, 15). Although purpura was absent, the platelets numbered only 30,000 per cubic millimeter. The urine contained much urobilinogen. The liver and spleen were greatly enlarged and showed "unusually marked myeloid metaplasia."

In the French literature the blood changes consequent on cancerous involvement of the bone marrow have long been known as the syndrome of Weil and Clerc.[77] The syndrome includes splenomegaly with or without hepatomegaly and almost always without adenopathy and ascites; blood smears show normal and abnormal nucleated erythrocytes, also myelocytes.

Faulds and Mackay [78] reported megaloblastic anemia with cancer. Harrington and Teacher [79] reported gastric cancer and extensive metastasis to the marrow with hyperchromic anemia and the constant presence of numerous myelocytes and erythroblasts. In neither case, however, can the infiltrative type of the tumor be assumed from the descriptions given. No data are given concerning the lungs.

Piney [80] stated that within the bone marrow the erythropoietic centers are intravascular and the leukopoietic centers are extravascular. Since the bone marrow lacks lymphatics, tumor cells can arrive by the hematogenous route only, and the metastases must first affect erythropoiesis and may later impair leukopoiesis.

Zadek and Sonnenfeld [81] considered the presence of normoblasts an indication of an irritation of the marrow by tumor and hence an important diagnostic sign.

Rawitsch and Warschawskaja [82] stated that only in metastatic carcinomatosis of the bone marrow is a mixed picture of violent erythrocytic and leukocytic regeneration seen. The presence of numerous immature erythrocytes has led to incorrect diagnoses of pernicious anemia, while the presence of immature leukocytes has simulated leukemia. The same problem is extensively discussed by Seemann and Krasnopolski.[2]

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77. Weil, P., and Clerc, A.: Semaine méd. **22**:373, 1902.
78. Faulds, J. S., and Mackay, W.: Lancet **2**:1334, 1927.
79. Harrington, A. W., and Teacher, J. H.: Glasgow M. J. **73**:241, 1910.
80. Piney, A.: Brit. J. Surg. **10**:235, 1922; **11**:707, 1923.
81. Zadek, I., and Sonnenfeld, A.: Klin. Wchnschr. **9**:2245, 1930.
82. Rawitsch, M. S., and Warschawskaja, B. B.: Folia haemat. **44**:150, 1931.

One lesion remains to be considered in relation to the anatomic and clinical complex under discussion. This lesion is the so-called Krukenberg tumor [83] of the ovary. At present it is believed that most if not all Krukenberg tumors are metastatic carcinomas, the primary growth being most often situated in the stomach.[84]

Krukenberg tumors have been mentioned as incidental findings in certain of the cases summarized in this paper.

Thus, the case of Terplan and Vaughan [70] showed a diffusely infiltrating carcinoma of the stomach, with lymphangitic metastases in the lungs, extensive metastases in the bone marrow, thrombocytopenia and pronounced erythroblastosis. The ovaries showed typical Krukenberg tumor. In the case of Stebbins and Carns [72] the stomach showed a depressed puckered nonindurated lesion simulating a peptic ulcer but showing carcinoma microscopically. Other findings in this case were lymphangitic carcinomatosis of the lungs, extensive metastases in the bone marrow and thrombocytopenic purpura. The authors state "lymphatic involvement was particularly noted in the ovaries and lungs."

Dupont and Lievre [85] reported the case of a woman aged 36 with clinically latent and widely infiltrating carcinoma of the stomach, lymphangitic carcinomatosis of the lungs, metastases in the bones and edema of the left arm. The ovaries showed Krukenberg tumor.

Graf [86] described briefly a case of recurrent mammary carcinoma. The viscera showed fine microscopic metastatic infiltrations. The lung contained no gross nodules but showed what was probably a lymphangitic type of tumor growth. Both ovaries were large and hard and were likewise finely infiltrated.

The case of Beger,[9] previously mentioned, was one of gastric carcinoma in a woman aged 20. This patient had lymphangitic carcinoma of the lung and also of the pelvic wall.

In 1927 my father, Dr. J. Jarcho,[87] reported seven cases of Krukenberg tumor. In all of the six cases in which autopsy was done a carcinoma of the stomach was found; all but one of these were fibrous or scirrhous carcinomas.[88] One case (no. 4) showed, in addition, lymphangitic carcinomatosis of the lungs.

GENERAL SUMMARY

The first part of this review is devoted to the anatomic and clinical characteristics of lymphangitic carcinomatosis of the lungs—a form of metastasis which has been virtually ignored in the English literature.

The second chapter summarizes those cases of carcinoma which are associated with purpura and thrombocytopenia. It is shown that in

83. Krukenberg, F.: Arch. f. Gynäk. **1**:287, 1896.

84. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

85. Dupont, A., and Lievre, J.: Ann. d'anat. path. **6**:335, 1929.

86. Graf, E.: Zur Kenntnis der Metastasenbildung bei Carcinomen, Dissert. Freiburg im Breisgau, Nürnberg, J. L. Stich, 1903.

87. Jarcho, J.: Am. J. Obst. & Gynec. **13**:288, 1927.

88. Janow, N. M.: Arch. f. klin. Chir. **163**:178, 1930.

almost every case of this kind, if the anatomic examination has been sufficiently thorough, deposits of tumor have been found in the bone marrow, and the lungs have shown lymphangitic metastasis, often associated with fine deposits of tumor within the smaller pulmonary blood vessels.

The third section demonstrates that lymphangitic pulmonary metastasis and the metastasis to bone marrow which is associated with purpura tend to occur in the same type of case—i. e., most often in the presence of flat diffusely infiltrating scirrhous and fibrous carcinoma, and especially in young adults; less often in older people or in the presence of extragastric primary carcinoma.

Since the two types of metastasis tend to occur simultaneously, it is inferred that they represent merely two aspects of the same process, which may be designated as diffusely infiltrative carcinoma. In any one instance both aspects of this process will usually be demonstrable at autopsy, whereas during life the clinical picture tends to be dominated by either hematopoietic or respiratory disturbances according to whether the marrow or the lungs are affected predominantly.

It is further shown that the disturbance of hematopoiesis in these cases need not always include purpura but may consist of (1) anemia, (2) signs of marked regenerative activity of both red and white cells, as shown by the presence of immature forms, (3) thrombopenia, (4) hepatosplenomegaly due to marked extramedullary hematopoiesis and (5) urobilinuria.

The complex of diffusely infiltrative carcinoma is further shown to include occasional instances of Krukenberg tumor of the ovary.

The complex picture of diffusely infiltrative carcinoma is thus shown to be an anatomic entity. On the anatomic side the regularity with which the component lesions are found to coexist is most striking in those cases which have been studied in greatest detail. On the clinical side interest is properly aroused by the subtle nature of the signs and symptoms, by the fine character of the lesions (which tend to elude palpation, percussion and especially roentgenographic examination) and by the rapid relentless progress of the malady.

The data thus assembled raise several important questions of pathogenesis, questions which are largely incapable of solution at the present time.

First it is necessary to consider what it is that gives rise to the peculiar diffusely infiltrative character of the tumors studied. This has been attributed to anaplasia or "unripeness."[2] According to this view, simple and scirrhous carcinomas composed of unconnected or loosely connected cells naturally present a greater tendency toward permeation of tissue spaces and lymphatics than the more highly specialized

solid carcinomas and adenocarcinomas.[89] This concept accords very well with the findings in my second case (see p. 688) and with such cases as that of Seemann and Krasnopolski,[2] Cosin[73] and Moon.[90] According to Fischer-Defoy and Lubarsch,[91] the size of implanted particles of tumor tissue may also play a rôle.

A striking anatomic feature of the cases under consideration here is the absence of the nodular forms of metastasis found in ordinary cases of carcinoma. In the present state of knowledge this peculiarity must be attributed vaguely to the biologic individuality of the tumor, and is perhaps to be regarded as a result of anaplasia. The widespread presence of tumor cells within blood vessels in many of the cases in the absence of nodular metastases suggests a fundamental antagonism between the tumor cells and the respective tissues. The nature of this antagonism can hardly be surmised at the present time.

Somewhat less intangible is the problem of the path of dissemination of the tumor cells. The most satisfactory explanation, that of von Meyenburg,[19] has been discussed in the first part of this study, and accounts for the pulmonic lesions only. Von Meyenburg suggested that tumor cells emanating from the stomach proceed to the abdominal nodes and thence to the mediastinal nodes. A stasis of lymph in the lungs is thereby engendered. This causes retrograde dissemination from the hilus toward the pleura. Actual observation, however, shows that tumor cells are present not only in the lymphatics of the lung but also occasionally in the blood vessels of the lung.[92] Cells might pass from the lymphatics into the circulating blood through the thoracic duct. Several of the cases have in fact yielded presumptive evidence of implication of the thoracic duct.[48]

At this point there is another hiatus in the evidence. Up to the present time lymphatics have not been demonstrated in the bone marrow.[93] Metastases in bone marrow must therefore be exclusively hematogenous. Hence it is necessary to assume that the tumor cells in passing from the thoracic duct into the greater circulation must pass through the lungs and again into the greater circulation, then into the bone marrow.

The hematologic disturbances which were recapitulated in the second part of the present study must be referred tentatively to actual destruc-

89. Kitain, H.: Virchows Arch. f. path. Anat. **238**:289, 1922. Seemann and Krasnopolski.[2]

90. Moon, V.: Arch. Path. **8**:938, 1919.

91. Fischer-Defoy, W., and Lubarsch, O.: Ergebn. d. allg. Path. u. path. Anat. **10**:850, 1906.

92. Cohen.[67] Herzog and Roscher.[68] Huguenin and others.[74]

93. Maximow, A.: A Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1931, p. 112. Piney.[80]

tion of bone marrow. This is due in part to actual occupation of marrow cavities by tumor and in part to fibrosis and hemorrhage. It is as yet impossible to assert with confidence that the thrombocytopenia is due to destruction or decreased megalokaryocytes, since quantitative studies were not instituted and, in addition, the origin of blood platelets has not been established beyond cavil.

These crude conjectures indicate the inchoate state of present knowledge of the subject.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Elmer E. Collins has been appointed assistant professor of pathology in Howard University, Washington, D. C.

Claus W. Jungblut has been promoted to the position of professor of bacteriology in the College of Physicians and Surgeons, Columbia University.

Edwin O. Jordan, professor emeritus of hygiene and bacteriology in the University of Chicago, has died at the age of 70 years.

W. W. Brandes has been appointed professor of pathology in the University of Tennessee, Memphis.

Kurt W. Franke, chemist at the South Dakota State College of Agriculture and Mechanic Arts, and well known for his important researches on selenium poisoning of cattle and other animals ("alkali diseases"), has died at the age of 47 years.

J. J. E. McWhorter, pathologist to the Englewood Hospital, Englewood, N. J., has died at the age of 51 years.

William Antopol has been appointed pathologist to the Beth Israel Hospital, Newark, N. J.

William Dock, a member of the department of medicine of the Stanford University School of Medicine, has been appointed professor of pathology in that institution. Associated with him as associate professor will be David A. Wood, and as assistant professors, James B. McNaught and Alvin J. Cox.

Hans Chiari has been appointed professor of pathology in the University of Vienna.

Oskar Klotz, professor of pathology and bacteriology in the University of Toronto, has died at the age of 58 years.

William B. Wherry, professor of bacteriology and hygiene in the University of Cincinnati, died Nov. 1, 1936, in his sixty-first year.

The Nobel Prize in physiology and medicine has been awarded to Sir Henry Dale, director of the National Institute of Medical Research, London, and to Otto Loewi, professor of pharmacology at Gratz, Austria, for their work on acetylcholine in innervation.

In the University of Toronto Thomas F. Nicholson has been promoted to the post of associate professor of pathology.

H. C. Kiehaupt, Vienna, died last summer after an illness of more than six years. Many Americans who studied medicine in Vienna will remember him as a teacher of German whose mastery of idiomatic expression was extraordinary.

Fiske Fund Prize Essay, 1937.—The trustees of this fund have proposed the following subject for 1937: "Newer Methods of Prevention and Treatment of Acute Anterior Poliomyelitis." For the best essay on the subject worthy of a premium they offer $250. Competitors must conform with the following regulations: The essayist must forward to the secretary on or before May 1, 1937, free of expense, a copy of his essay, with a motto thereon, accompanied by a sealed envelop with the same motto on the outside and his name and address within. The essay must be typewritten and should not exceed 10,000 words. The author of the successful essay must transfer all his right, title and interest in the same to the Fiske Fund. For further details address Dr. Wilfred Pickles, secretary, 184 Waterman Street, Providence, R. I.

Correspondence

CAPILLARY CIRCULATION TO ATHEROSCLEROTIC LESIONS

October 16, 1936.

To the Editor:—May I correct the misinterpretation of my work conveyed in a reference in the paper of Dr. J. C. Paterson entitled "Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries" in the September issue of the ARCHIVES OF PATHOLOGY (**22**:313, 1936)? The reference is as follows: "Leary [3] (ARCH. PATH. **17**:453, 1934) described proliferating intimal capillaries in four of twenty-one cases of coronary thrombosis and in at least one of these serial sections revealed a discrete opening of a capillary into the lumen. Leary made no comment on this finding; in fact in a later paper [4] (*Am. Heart J.* **10**:328, 1935) he doubted the existence of a true blood supply to atherosclerotic plaques."

In the first paper referred to (ARCH. PATH. **17**:453, 1934) twenty-one cases of coronary sclerosis, not thrombosis, were used to illustrate the contrasting types of coronary lesions arising in youth and at older ages in connection with sudden deaths. Fresh thrombi were found in fifteen cases only in this series.

In the younger group showing the youthful reaction there was reported for the first time a capillary circulation derived from the coronary lumen. The connections of this system with the lumen were demonstrated not in one but in four coronaries in this younger group. Photomicrographs were published not of one but of two capillaries connecting with the coronary lumen. Another four of this group of ten coronaries with the youthful reaction had capillary systems derived from vasa vasorum.

The only possible basis for the inference that I "doubted the existence of a true blood supply to atherosclerotic plaques" is a sentence in a paragraph dealing specifically with the formation at older ages of atherocheumas (so-called atheromatous "abscesses"). These lesions are due to the piling up of lipoid cells without adequate provision for their nutrition. I stated: "There is no true vascularization of the cell masses" (*Am. Heart J.* **10**:328, 1935). The standard outcome of the piling up of these cells, i. e., nutritive necrosis with the formation of atherocheumas, is the best evidence that this statement is justified. Its limitation to this field is also evident. Capillary circulations to atherosclerotic lesions from vasa vasorum become common as the lesions age and enlarge.

TIMOTHY LEARY, M.D., Boston.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Splenohepatomegaly Associated with Widespread Hyperplasia of Non-lipoid-Storing Macrophages (Letterer-Siwe's Disease). A. F. Abt and E. J. Denenholz, Am. J. Dis. Child. **51**:499, 1936.

Abt and Denenholz report the occurrence in an infant of splenohepatomegaly, generalized lymphadenopathy, cutaneous hemorrhages, anemia and widespread hyperplasia of nonlipoid-storing macrophages in the liver, spleen, lymph glands, bone marrow and lungs. Eight similar cases have been recorded in the literature —the first by Letterer in 1924.

Local Immunization of the Lungs of Guinea-Pigs Against the Tubercle Bacillus. R. L. Ferguson and P. R. Cannon, Am. Rev. Tuberc. **33**:328, 1936.

Guinea-pigs were immunized intratracheally with a phenol-killed culture of the tubercle bacillus (H37) and infected intratracheally some weeks later with living organisms of the same strain. The intratracheal immunization conferred increased resistance and favored mobilization of macrophages in the interstitial tissue and in the regional lymph nodes. The results support the idea that direct antigenic stimulation of a portal of entry may increase resistance against the infectious agents entering by the same route.

H. J. Corper.

Hyperthermia Due to Lesions in the Hypothalamus. B. J. Alpers, Arch. Neurol. & Psychiat. **35**:30, 1936.

The hypothalamus seems to be the most important center of so-called heat regulation, though the nervous mechanism of the latter seemingly extends from the cortex to the medulla, also implicating the corpus striatum, midbrain, pons and medulla. Alpers made serial sections of the hypothalamis from two patients who died from supracellar cysts with hyperthermia. In the first patient the tumor extended from the pituitary body to the anterior border of the pons, and the entire floor of the brain in this region was covered with blood, which destroyed the substantia grisea and isolated portions of the nucleus tuberomamillaris. In the second patient, who had a cyst of the pituitary fossa beneath the chiasm, there was also in evidence destruction of the floor of the third ventricle with involvement of the substantia grisea and of parts of the tuber cinereum. Alpers states that the areas mentioned may also produce hypothermia, and that hyperthermia is the result of "irritation" of the center of heat production located in the substantia grisea of the third ventricle.

George B. Hassin.

Are There Cyclic Changes in the Human Vaginal Mucosa? B. Zondek and M. Friedmann, J. A. M. A. **106**:1051, 1936.

Zondek and Friedmann report that the human vaginal mucosa does not reveal cyclic changes analogous to those of the uterine mucosa. The vaginal mucosa shows different microscopic pictures in different places. The picture with deficient ovarian function (primary amenorrhea) is similar to that with good ovarian function, and even the changes in the premenstrual phase are the same. In the absence of ovarian function, the authors could produce enlargement of the uterus, proliferation and the premenstrual condition of the uterine mucosa and menstruation by means of ovarian hormones (estrogenic substance, progestin) but not analogous changes in the vaginal mucosa. The infantile vagina may be influenced

by estrogenic substance, but it is not certain whether it is because of a specific hormonal effect on the vaginal mucosa or because of an effect on the mucous membranes in general. Since the vagina is developed embryologically differently in different species, the different reaction of the vaginal mucosa is explainable.

FROM THE AUTHORS' SUMMARY.

THE RELATION OF THE HYPOPHYSIS TO THE SPLEEN. D. PERLA, J. Exper. Med. **63**:599, 1936.

In adult rats removal of the hypophysis is followed by progressive atrophy of the spleen. At the end of two months the ratio of spleen weight to body weight is one-half the normal. Administration of an emulsion of the hypophysis leads to a considerable degree of repair of the spleen in such animals. Hypophysectomy completely inhibits the regeneration of splenic tissue after partial splenectomy. Administration of an emulsion of the anterior lobe of the hypophysis restores this regenerative capacity in the hypophysectomized rat. Daily administration of an emulsion of the anterior lobe of the hypophysis of cattle or of an alkaline extract of fresh or acetone-dried anterior lobe during a period of ten days to a normal bartonella carrier or bartonella-free rat results in hypertrophy of the spleen to twice the normal size. Normal rats receiving the emulsion during a period of one month become refractory to the spleen-stimulating effect. At the end of this period the spleen shows little increase in size above the normal. Injections of horse serum or of alkaline extract of acetone-dried kidney, spleen or liver of cattle did not cause splenic enlargement in rats of bartonella-free stock. The increase in the size of the spleen following daily administration of an emulsion of the anterior lobe of the hypophysis is due primarily to marked hyperplasia of the reticular and endothelial cells of the red pulp. The follicles also increase in size. Clusters of reticular cells containing numerous lymphoid elements appear throughout the pulp. The reticular tissue of the bone marrow is similarly increased. There is a striking increase in the number of hemocytoblasts and megakaryocytes. The Kupffer cells are not affected. The spleen-stimulating factor is not present in the acid extract of the anterior lobe of the hypophysis, the extract that contains thyrotropic and adrenotropic factors. It is present in some degree in the alkaline extract of fresh anterior lobe, the extract containing growth and gonadotropic factors. It is also present in the alkaline extract of acetone-dried anterior lobe relatively free from the growth hormone. The presence of a spleen-stimulating factor in the anterior lobe of the hypophysis is suggested by these experiments.

FROM THE AUTHOR'S SUMMARY.

EFFECTS OF VAGOTOMY ON THE GASTRIC FUNCTIONS OF MONKEYS. J. B. FERGUSON, Surg., Gynec. & Obst. **62**: 689, 1936.

Following complete severance of the vagus nerves either in the neck or beneath the diaphragm cardiospasm of a persistent type occurred. There was evidence of gastric hypotonia and of delay in the onward passage of solid foodstuffs. The acid tide following a test meal was not lowered in the animals subjected to fractional gastric analysis. Only a slight rise occurred in the intraventricular threshold for the anacidity effect which previously had been found as a typical response to injections of the parasympathomimetic drugs, pilocarpine hydrochloride and acetyl-β-methylcholine hydrochloride. Two animals showed mucosal erosions at autopsy, one in the stomach and the other in the duodenum, the latter leading to death of the animal.

FROM THE AUTHOR'S SUMMARY. (WARREN C. HUNTER.)

A DISEASE OF SPONGE DIVERS. S. G. ZERVOS, Paris méd. **2**:79, 1934.

The disease described by Zervos and sometimes called by his name occurs among the sponge divers off the coast of Calymos. It is caused by the venom of the actinium, a member of the sea anemone group, which is found on the roots

of sponges. The sting of the animal causes a necrotic, suppurating lesion which takes weeks to heal and leaves a big scar. Within several hours after injection of the poison the patient experiences headache, chills, fever and vomiting. The effect is seldom fatal, local treatment proving effective. No neutralizing agent for the venom has been found.

ELIZABETH MCBROOM.

THE INFLUENCE OF REPEATED INJECTIONS OF BLOOD AND OF SPLENIC EXTRACT ON THE LEUKOCYTE COUNT OF THE RABBIT. P. BERGSTRÄSSER, Frankfurt. Ztschr. f. Path. **47**:262, 1935.

Rabbits were given (1) repeated intramuscular injections of untreated autogenous blood, (8) defibrinated sheep blood, (3) citrated autogenous blood and (4) commercial splenic extract. Injections were given at the rate of one every two days over a period of from four to eight weeks. The results in the four series were similar. An increase of the white blood cells was always observed. This increase was least marked in the series receiving foreign blood, contrary to the experience of other authors. The basophilic leukocytes did not increase in number after injections of autogenous untreated blood but increased after the use of the three other materials, most markedly after injection of the splenic extract. The monocytes increased in similar proportions. The most marked stimulation of bone marrow was produced by the splenic extract.

OTTO SAPHIR.

EXPERIMENTAL ALLERGIC INFLAMMATION OF THE MENINGES. A. SSOLOWJEW and M. B. ARIEL, Virchows Arch. f. path. Anat. **295**:201, 1935.

Rabbits were sensitized by suboccipital injections of normal horse serum into the subarachnoid space. The meningeal reaction in controls receiving only the sensitizing injections and in animals that received the activating injection was studied histologically. Anaphylactic shock did not occur in any of the animals. In thirteen of the sixty animals used a hyperergic inflammatory reaction of the leptomeninges was observed. The reaction was diffuse. In addition to cellular infiltration, hyaline thrombosis and hyaline fibrinoid degeneration of the adventitia of vessels were observed.

O. T. SCHULTZ.

Pathologic Anatomy

JEJUNAL DIVERTICULOSIS. R. S. ROSEDALE, Surg., Gynec. & Obst. **61**:223, 1935.

Diverticulosis of the jejunum is rare, only 3 instances having been found in 5,000 autopsies at the Buffalo City Hospital. Sixteen cases of acquired diverticula of the small intestine have been recorded in a series of 14,068 autopsies in Dresden, Germany. In one case studied by Rosedale there were both jejunal and colonic diverticula. Another, the second such example recorded, presented in addition to jejunal diverticulosis an infestation with Taenia saginata. As a rule, diverticula of the jejunum are symptomless, and nearly all instances are discovered at operation or necropsy. The etiology is obscure.

WARREN C. HUNTER.

HYPEROSTOSIS FRONTALIS INTERNA. SHERWOOD MOORE, Surg., Gynec. & Obst. **61**:345, 1935.

The term was first employed by Moore and by Morel almost simultaneously to designate a peculiar condition occasionally found in the frontal bone, associated with which were mental disturbances and obesity. The lesion is by no means the medical curiosity that statistics appear to make it, for to the sixty-five cases recorded in the literature seventy-two other examples have been added. Regionally, the cases can be classified into those in which the hyperostosis is confined to the squamous portion of the frontal bone, those in which it is confined to the orbital

plate, and those in which it occurs in both these portions. The other bones of the cranium appear not to be involved. The thickening of the frontal bone does not extend beyond the coronal suture. The outer table of the skull remains unaltered, but the diploe appears to be diminished or obliterated according to the degree of hyperostosis. The process differs, roentgenographically at least, from other involvements of bone in that there is no porosity or loss of calcium, so that it is reasonable to suppose that it is a disorder of calcium metabolism in which that mineral is presented in excess in the body. In spite of the different degrees or types of the disorder, the cases have an astonishing similarity to each other and vary only in the intensity of the symptoms. Thus far only hypotheses as to the cause of the process have been advanced. The disease will be found with far greater frequency when it is sought for by roentgenologists as a routine. The descriptive name at present employed for the syndrome suffers from the drawback inherent in using a single feature of a disorder to designate the whole. The hyperostosis, while the surest sign of the disease, may be the least important of its manifestations.

WARREN C. HUNTER.

THE GOLGI APPARATUS OF SYNOVIAL CELLS. E. S. J. KING, J. Path. & Bact. **41**:117, 1935.

A well developed Golgi apparatus is readily demonstrated in human synovial tissues and with greater difficulty in those of the horse and dog, comparable with that of other connective tissue cells. This structure becomes enlarged in conditions in which there is increased production of synovial fluid. Cells free in the synovial fluid, many of them recognizable as synovial cells, also show a well formed Golgi apparatus. Since the Golgi apparatus is not demonstrable in degenerative states, its well developed character in these cells indicates that synovial fluid and the material found in ganglions, etc., are not products of degeneration.

FROM THE AUTHOR'S CONCLUSIONS.

PSEUDOTUBERCULOMA SILICOTICUM. J. S. FAULDS, J. Path. & Bact. **41**:129, 1935.

Two cases of subcutaneous pseudotuberculoma are described, caused by the implantation of silicious material and not by the tubercle bacillus. The cases are similar to the one described by Shattock under the name of pseudotuberculoma silicoticum. The advantage of the examination of the material by polarized light is demonstrated.

FROM THE AUTHOR'S SUMMARY.

THE LOCAL FORMATION OF BLOOD PIGMENTS. R. MUIR and J. S. F. NIVEN, J. Path. & Bact. **41**:183, 1935.

In mice and rats the formation of granular and crystalline pigment from erythrocytes injected subcutaneously is intracellular. Phagocytosis of erythrocytes is followed by rapid formation of hemosiderin, evident from twenty-four hours onward after the injection of the blood cells. The hemosiderin is found in both diffuse and granular forms. These changes go on till all the erythrocytes are disposed of. Formation of hematoidin is first seen at about the seventh day and may occur in two ways: *(a)* in cells containing hemosiderin a few crystals first appear, and then their number increases; *(b)* in cells which have a bright yellow protoplasm and give no iron reaction hematoidin often forms rapidly in a massive fashion by crystallization from the diffuse yellow pigment. The yellow pigment and the crystals give the Gmelin reaction for bile pigment. The interpretation made is that the diffuse yellow pigment is formed from hemosiderin, the iron being apparently discharged in some form. The changes following injections of hemoglobin are of a corresponding nature. Iron reaction of a diffuse character may be detected in cells within twenty-four hours, and granular hemosiderin appears later. The formation of hematoidin crystals may be observed on the seventh day and takes place in cells containing hemosiderin; at a later period it may be relatively

abundant. No formation of granular or crystalline pigments has been observed outside cells. In rabbits the formation of hematoidin has not been observed after injections of erythrocytes or hemoglobin. (See also Niven, J. S. F.: The Formation of Haematoidin in Vitro, ibid., p. 177.)

FROM THE AUTHORS' CONCLUSIONS.

THE NEUROGLIA IN STATUS EPILEPTICUS. M. GÓRRIZ and A. P. RODRIGUEZ PÉREZ, Trav. du lab. de recherches biol. de l'Univ. de Madrid **29**:307, 1934.

The authors made a study of the changes in the neuroglia in the brains of three patients who died in status epilepticus. The neuroglia were demonstrated by the gold sublimate method of Cajal. The changes were degenerative, with disintegration of the bodies of the astrocytes, rupture and fragmentation of their prolongations, and formation of ameboid cells.

CYRIL B. COURVILLE.

HYPERTROPHY OF THE PROSTATE. A. KROGIUS, Arb. a. d. path. Inst. d. Univ. Helsingfors **8**:1, 1935.

Hypertrophy of the prostate should be considered as a hyperplastic regenerative process which forms new glandular parenchyma. The growth of prostatic hypertrophy, just as the normal process of prostatic regeneration, has its origin from the epithelium of the excretory ducts, which, even in old age, maintains its power to produce new glandular tissue. Prostatic hypertrophy owes its special character to the fact that the hyperplasia takes place primarily in the middle lobe. The growth of the periglandular connective tissue which accompanies hypertrophy of the glandular tissue is much greater in the thick fibromuscular stroma of this region than in the lateral lobes and furnishes a matrix into which new glands may grow. In the same fashion small adenofibromas arise; subsequently displacing the surrounding connective tissue, they give rise to the nodular structure characteristic of hypertrophy of the prostate. As it concerns pathologic changes, the growth finally causes deformity of the lumen of the urethra and mutually compressing glandular nodules. The nonglandular nodules arise from the periglandular connective tissue. The epithelial lining of the newly formed tubules soon develops into a mature and secreting epithelium of the apocrine type which elaborates an apparently normal prostatic secretion. With the progressive enlargement of the nodules, however, there often results a compression of the ducts, so that in the more advanced stages of the disease the secretion of the prostate practically ceases and a retrogressive change sets in with dilatation and cyst formation. In its mode of development and its structure, prostatic hypertrophy is analogous in many ways to chronic cystic mastitis.

FROM THE AUTHOR'S SUMMARY. (CHARLES E. DUNLAP.)

FOREIGN BODY INCARCERATED IN THE ESOPHAGUS. G. GAEHTGENS, Centralbl. f. allg. Path. u. path. Anat. **63**:5, 1935.

A coin (10 *Pfennigstück*) was found in the esophagus of a child 1½ years old who died of myocarditis following pharyngeal diphtheria. There were no history of the coin's being swallowed and no symptoms referable to such an act, which must have occurred a considerable time before the terminal illness. The coin was firmly embedded in the esophageal mucosa, on the anterior part between the cricoid cartilage and the bifurcation. Although it was embedded so deeply that it was removed with difficulty, there was no erosion of the tracheal cartilage.

GEORGE RUKSTINAT.

DISEASES OF THE HEMATOPOIETIC SYSTEM IN A LARGE GENERAL HOSPITAL. A. F. ZANATY, Virchows Arch. f. path. Anat. **294**:315, 1935.

From his work in the Charité-Krankenhaus in Berlin Zanaty received the impression that diseases of the hematopoietic system are more frequent in Berlin

than in his homeland, Egypt. He therefore tabulated these diseases as encountered in a total of 15,141 necropsies done in the eleven years from 1923 to 1933. The total number of necropsies included necropsies on 2,361 stillborn infants, premature infants and children under 1 year of age. The diseases of the blood-forming organs were as follows: leukosis, 164 cases, subdivided into 81 cases of myelosis and 83 of lymphadenosis; lymphogranulomatosis, 70 cases; pernicious anemia, 119 cases; other anemias, 21 cases; agranulocytosis, 10 cases, all recorded since 1928; reticuloendotheliosis, 52 cases, of which 31 had occurred since 1930, suggesting a more proficient recognition of this type of disease. In the age period from 1 to 15 years there were 2,814 cases of disease of the hematopoietic system, and in that above 15 years, 9,928. These are analyzed further as to sex and decade of life. Two atypical cases are presented to illustrate that a correlation of clinical and pathologic-histologic observations is necessary for a proper evaluation of diseases of the blood-forming organs.

O. T. SCHULTZ.

AMYLOIDOSIS OF CEREBRAL VESSELS. Z. I. MORGENSTERN, Virchows Arch. f. path. Anat. **294**:334, 1935.

Amyloidosis of cerebral vessels has been said not to occur. Morgenstern reports a case of localized amyloidosis of cerebral vessels associated with meningioma. The process was limited to the vessels of the tissue adjacent to the tumor.

O. T. SCHULTZ.

INTESTINAL NECROSIS IN HYPERTENSION AND UREMIA. K. SPANG, Virchows Arch. f. path. Anat. **294**:340, 1935.

Spang describes an instance of hemorrhagic necrosis of the small intestine associated with malignant nephrosclerosis, and two of uremic enteritis associated in one case with secondary contracted kidney and in the other with malignant nephrosclerosis. In the first case microscopic examination revealed sclerosis, necrosis and obliteration of arterioles of the intestine. In the second case there were no intestinal vascular changes and in the third only arteriolar sclerosis. In the first and third cases the intestinal changes are ascribed to the vascular changes, which were the result of hypertension. The second case was one of true uremic enteritis due to renal insufficiency and the excretion of toxic materials into the intestine. The author therefore concludes that what has been termed uremic enteritis is not a single entity but may be due to arteriolar changes similar to those encountered in the other organs.

O. T. SCHULTZ.

Microbiology and Parasitology

DIPHTHERITIC MENINGITIS. F. G. CARLSON and H. W. MORGAN, J. A. M. A. **106**:1164, 1936.

In a case of fatal meningitis due to Klebs-Löffler bacilli inoculation of guinea-pigs showed the organism to be of a virulent strain. No similar cases could be found described in the English literature. The German literature contains reports of four cases. In the case reported the disease followed otitis media and mastoiditis.

FROM THE AUTHORS' SUMMARY.

INFECTIOUS FIBROMA OF RABBITS. R. E. SHOPE, J. Exper. Med. **63**:33 and 43, 1936.

Serial Transmission of Virus Myxomatosum in Cottontail Rabbits and Cross-Immunity Tests with the Virus of Fibroma.—Virus myxomatosum injected into the testicles of cottontail rabbits was observed to produce only localized fibromatous or myxomatous orchitis. This was quite unlike the acute fatal illness which the virus caused in domestic rabbits. Ten serial passages of the virus through cotton-

tail rabbits, covering one hundred and forty days, failed to alter its pathogenicity for domestic rabbits. Although it proved impossible to convert the virus into fibroma virus by serial passage in cottontail rabbits, it was found that these animals on recovery from myxoma were solidly resistant to the fibroma virus. Furthermore, their serums possessed antibodies neutralizing the fibroma virus as well as virus myxomatosum. A similar cross-immunity was observed in domestic rabbits that had survived an attack of infectious myxoma.

Virus Myxomatosum Infection of Rabbits Recovered from Fibroma.—The serial passage of virus myxomatosum through domestic rabbits that had recovered from fibroma did not alter its pathogenic properties. In the inoculated testicles of these rabbits the virus persisted fully virulent for at least sixteen days following inoculation The same virus injected into the testicles of myxoma-immune domestic rabbits, on the other hand, was promptly rendered nondemonstrable. The failure of domestic rabbits that had recovered from fibroma to destroy injected virus myxomatosum and the absence from their serums of neutralizing antibodies effective against this virus are considered to be evidence against the identity of the fibroma and myxoma viruses. The rapidity with which neutralizing antibodies develop in rabbits that have recovered from fibroma following infection with virus myxomatosum is considered to be a possible factor in their acquired resistance. On the basis of all the evidence it is believed that infectious fibroma of rabbits is a definite disease entity and not merely a mild, nonfatal form of infectious myxoma.

FROM THE AUTHOR'S SUMMARY.

MENINGITIS IN MAN CAUSED BY A FILTERABLE VIRUS. T. M. RIVERS and T. F. M. SCOTT, J. Exper. Med. **63**:397 and 415, 1936.

A virus was obtained from the spinal fluid of two patients with bacteria-free lymphocytic meningitis. The immunologic evidence indicates that this virus is identical with the Armstrong-Lillie and the Traub virus.

THE LIMITED NEUROTROPIC CHARACTER OF THE ENCEPHALITIS VIRUS (ST. LOUIS TYPE) IN SUSCEPTIBLE MICE. L. T. WEBSTER and A. D. CLOW, J. Exper. Med. **63**:433, 1936.

St. Louis encephalitis virus injected intracerebrally into susceptible mice multiplies there to a titer of 10^9 intracerebral lethal doses. It is found also in the blood in small amounts immediately following injection and preceding death. Injected intraperitoneally or subcutaneously the virus circulates in the blood for several hours and survives in the spleen for days. It does not multiply in the brain and cause encephalitis, however, unless overwhelming doses are injected or the brain is traumatized. Virus dropped into the nares is demonstrable in the olfactory bulbs at twenty-four hours, in the pyriform lobes at from twenty-four to forty-eight hours, in the remainder of the brain at three days and in the spinal cord at four days. In the brain it reaches a titer of 10^9 in six days. The virus is not readily demonstrable in the blood but is present in the spleen after forty-eight hours. The virus survives and is capable of multiplying in the spleen. Lesions following nasal instillation of the virus appear first in the olfactory bulbs, on the third day, in the pyriform lobes on the fourth and in Ammon's horn on the fifth day. The developmental phases in the order of their appearance, are exudation of mononuclear cells about superficial blood vessels and in the pia, hyperplasia of the endothelium of the pia and necrosis of nerve cells of the olfactory tract.

FROM THE AUTHORS' CONCLUSIONS.

INAPPARENT (SUBCLINICAL) INFECTION OF THE RAT WITH LOUPING-ILL VIRUS. F. M. BURNET, J. Path. & Bact. **42**:213, 1936.

Rats show no evidence of infection after intranasal inoculation of the virus of louping ill, but the virus regularly appears and apparently multiplies in the olfactory bulbs. It disappears from the olfactory bulbs after the eighth or ninth day

concomitantly with the appearance of virus-inactivating antibodies in the serum. As a rule, no further spread of the virus into the central nervous system beyond the olfactory bulbs occurs. In rare instances traces of the virus may be found in other parts of the brain. Splenectomized rats suffering from bartonella anemia show the same reactions as normal rats to intranasal inoculation of the virus of louping ill. Roentgen-irradiated rats appear to be a little more susceptible to the spread of the virus into the central nervous system than normal animals. The susceptibility of the first and second olfactory neurons to the virus is discussed in relation to the processes involved in subclinical infection and immunization by neurotropic viruses such as that of poliomyelitis.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTS WITH ISOLATED INCLUSION BODIES OF FOWL POX AND ECTROMELIA. GERTRUD BAUMGARTNER, Zentralbl. f. Bakt. (Abt. 1) **133**:282, 1935.

Inclusion bodies were isolated from lesions of fowl pox and ectromelia by microdissection and injected into susceptible fowls and mice, respectively. The injection into each animal of a single inclusion body suspended in a virus-free fluid yielded positive results in 46 per cent of the fowls and 42 per cent of the mice. The results with fowl pox confirm the results of Goodpasture and Woodruff.

PAUL R. CANNON.

LACTIC ACID BACILLI FROM THE VAGINA, THE NURSLING'S INTESTINE AND THE TEETH. HEINZ REPLOH, Zentralbl. f. Bakt. (Abt. 1) **133**:332, 1935.

Lactic acid bacilli were isolated from the vaginas of normal pregnant women, from carious teeth and from stools of nurslings in broth containing 2 per cent dextrose and 0.5 per cent acetic acid. The cultures were compared in various ways. Reploh could find no typical differences and concludes that they are all essentially of the Bacillus acidophilus group.

PAUL R. CANNON.

RICKETTSIAE IN ORGANS OF MICE INFECTED WITH THE VIRUS OF MANCHURIAN AND JAPANESE TYPHUS. S. KASAHARA, S. YOSHIDA and Y. OKAMOTO, Zentralbl. f. Bakt. (Abt. 1) **133**:406, 1935.

Emulsions of material containing the virus were injected intraperitoneally into mice, and smears of the tunica vaginalis testis, omentum, spleen, liver, lung, kidney, adrenal gland, testicle, mesenteric lymph nodes, endocardium and bone marrow were fixed in methyl alcohol and stained by Giemsa's method. Rickettsiae were shown in large numbers in all. A large amount of highly virulent virus-containing material must be injected, however. The experiment is unsuccessful if the external temperature is high (summer heat) or if the virulence of the virus is weak.

PAUL R. CANNON.

Immunology

INFECTIOUS MONONUCLEOSIS. I. DAVIDSOHN, Am. J. Dis. Child. **49**:1222, 1935.

The value of the test for heterophilic antibodies for the diagnosis of infectious mononucleosis is discussed, and a case is reported in which the test permitted differentiation of the disease from acute appendicitis. The changes in the blood picture and in the titers of agglutinins and hemolysins for sheep erythrocytes and in those of agglutinins for rabbit erythrocytes were followed for more than four months. A description of the histologic details of an enlarged lymph node is included. A new technic of the agglutination test for heterophilic antibodies in infectious mononucleosis is described, and its advantages over the old technic are discussed. The new test permits reading the end-results in two hours.

I. DAVIDSOHN.

IMMUNITY TO THE VIRUS OF MUMPS IN MONKEYS. C. D. JOHNSON and E. W. GOODPASTURE, Am. J. Hyg. **23**:329, 1936.

Evidence is presented that the only reliable experimental method of inducing active immunity to mumps in monkeys is that of causing a unilateral or bilateral clinical or subclinical specific parotitis by intraparotid inoculation. Some monkeys prove to be immune to intraparotid injection of the virus of mumps following the use of oral and nasal sprays of suspensions of the virus or after subcutaneous, intramuscular or intravenous injections of the virus; but these methods often fail to immunize. Attempts to confer passive immunity by injections of serum from persons immune to mumps have with rare exceptions failed. There are indications that the virus of mumps may infect the nerve tissue of monkeys after intracerebral injection. Immunity to infection from intraparotid injection of the virus has followed quite regularly a single intracerebral injection.

FROM THE AUTHORS' SUMMARY.

THE IMMUNIZATION OF GUINEA-PIGS WITH HEAT-KILLED AND FORMOL-KILLED TUBERCLE BACILLI. ARNOLD BRANCH and JOHN F. ENDERS, Am. Rev. Tuberc. **32**:595, 1935.

In accordance with the results of earlier observations, young cultures of virulent tubercle bacilli killed by heat (at 65 C.) have given satisfactory results as a prophylactic vaccine in guinea-pigs. The intramuscular route proved more efficacious than the intravenous or the intraperitoneal route. Organisms killed by formaldehyde (solution of formaldehyde U. S. P. in 0.25 per cent dilution) were no more effective than heat-killed bacilli. No correlation was found between the degree of cutaneous reactivity of individual animals to tuberculin following vaccination before infection and their period of survival after infection (immunity).

H. J. CORPER.

CHANGES IN THE MACROPHAGE SYSTEM OF THE LUNGS IN LOBAR PNEUMONIA. O. H. ROBERTSON and C. G. UHLEY, J. Clin. Investigation **15**:115, 1936.

Tissues from forty patients who died of lobar pneumonia were studied with the purpose of ascertaining whether or not the macrophages play as conspicuous a part in the later stages as they do in experimental lobar pneumonia in the dog. It was found that resolution of the consolidated lung was accompanied by changes in the parenchyma and in the cellular exudate analogous to those occurring in the dog's lung at the time of recovery. The evolution of the whole process could be followed often in a single case when lesions of different ages were present. The first evidence of the reaction is an increase in the number of large mononuclear cells in the alveolar walls, many of which protrude into the air spaces. As the process develops, the large mononuclear cells become detached from the alveolar wall and enter the exudate, where they exhibit the form and phagocytic functions of the macrophages. These cells gradually replace the polymorphonuclears, the fibrin disappears and the lesion assumes the characteristic appearance of resolution. The same type of reaction was observed in the lymph nodes at the hilus of the lung; sections from six patients who died from six days to two months after recovery from lobar pneumonia showed a pronounced macrophage reaction. Whenever a well developed macrophage reaction occurred, pneumococci were few or absent, whereas they were abundant in the majority of lesions of all ages in which the exudate was composed predominantly of polymorphonuclear leukocytes. Such marked differences in numbers of pneumococci were observed not only between lobar lesions but also at times in different parts of the same lesion in areas of which focal macrophage reaction was occurring. The macrophages were seen to be actively phagocytic and gave evidence of effective digestion of engulfed pneumococci.

FROM THE AUTHORS' SUMMARY.

THE NATURE OF THE HETEROPHILIC ANTIBODIES IN INFECTIOUS MONONUCLEOSIS. I. DAVIDSOHN and P. H. WALKER, Am. J. Clin. Path. **5**:455, 1935.

Serums from eleven patients with horse serum disease, from seven with infectious mononucleosis, from two with borderline conditions which resembled infectious mononucleosis clinically and hematologically, and from normal controls were treated with sheep erythrocytes and with suspensions of the kidney of the guinea-pig, the rabbit and the horse. The effect of the absorptions on the titers of agglutinins for sheep erythrocytes demonstrated the differences of the latter antibodies in infectious mononucleosis and in serum disease. In the former they are not of the Forssman heterophilic type. The erythrocytes of the sheep and the kidney of the horse contain a new type of heterophilic antigen in addition to the Forssman type. The new antigen reacts with the antibody in the serum of patients with infectious mononucleosis. A technic of absorption is presented which permits a ready differentiation of infectious mononucleosis from serum disease and from conditions simulating infectious mononucleosis clinically and hematologically.

I. DAVIDSOHN.

DISTRIBUTION OF BLOOD GROUP SPECIFIC SUBSTANCES AND BLOOD GROUP ENZYMES IN THE GASTRO-INTESTINAL TRACT. E. WITEBSKY and E. NETER, J. Exper. Med. **62**:589, 1935.

Group-specific substance A is present in the contents of the jejunum and upper part of the ileum in persons belonging to blood group A. In adults a marked decrease in the amount of this substance occurs in the lower part of the ileum and in the cecum, while the contents of the colon and rectum are more or less free from it. The agent destroying the group substance first appears in the lower part of the ileum or in the cecum, and its effectiveness increases in the lower parts of the large intestine. In two cases of intestinal obstruction this agent could be demonstrated in the contents of the jejunum and ileum.

FROM THE AUTHORS' SUMMARY.

THE TOXIN PRODUCTION OF THE SHIGA BACILLI. E. WAALER, J. Exper. Med. **63**: 1, 1936.

The S, R and R_a variants of the Shiga bacillus are equally toxic. The effect of the toxin on rabbits is the same whether it is obtained from filtrates of broth cultures (from three to six days old) or by autolysis of the killed bacteria grown on an agar surface. In both cases the rabbits show prostration, loss in weight, paralysis and diarrhea. When the toxin is heated to 80 C. for one hour, its poisonous effect nearly disappears, but its immunizing ability is unaltered. The heated toxin induces formation of an antitoxin which can protect against the unheated toxin. The anatomic changes observed in the spinal cord (degeneration of the motor neurons) and in the cecum (hyperemia and hemorrhages) are in agreement with the observations of previous authors. Furthermore, the toxin causes hyperemia and hemorrhages in the heart and hyperemia and degeneration in the kidneys and the liver.

FROM THE AUTHOR'S CONCLUSION.

INHIBITION OF THE SHWARTZMAN PHENOMENON. T. OGATA, J. Exper. Med. **63**:59, 1936.

The Shwartzman phenomenon can be inhibited by injecting intravenously a potent bacterial filtrate within a few hours before or after the preparatory intradermal injection. The inhibitory effect is produced nonspecifically by filtrates potent in the elicitation of the Shwartzman phenomenon, and the effect is transitory. The relation of the observation to anaphylactic desensitization and to its clinical significance is discussed in this paper.

FROM THE AUTHOR'S SUMMARY.

INVESTIGATIONS OF VACCINE VIRUS. R. F. PARKER and T. M. RIVERS, J. Exper. Med. **63**:69, 1936.

Humoral antibodies and a certain degree of resistance to vaccinia, probably not enduring, are produced in rabbits by repeatedly injecting inactive formaldehydized (0.3 per cent) elementary bodies of vaccinia and virus-free filtrates of dermal vaccine virus. A single injection of a large amount of elementary bodies is not so effective as a similar amount administered in small repeated doses. Drastic treatment with 10 per cent formaldehyde or by boiling for two hours almost completely alters or destroys the antigenicity of elementary bodies. It appears that the production of precipitins and agglutinins does not parallel that of neutralizing antibodies and that the mere presence of such antibodies in the serum of a rabbit as the result of injections of inactive elementary bodies does not necessarily indicate that the animal possesses a great degree of resistance to a potent vaccine virus. The fact that some neutralizing antibodies appeared in the serums of rabbits that had received injections of inactive elementary bodies can be interpreted as indicating that at least not all neutralizing antibodies for vaccine virus are the result of a reaction to an antigen produced by the host in consequence of a vaccinal infection. No evidence was obtained to show that elementary bodies inactivated by our methods (i. e., with 0.3 per cent formaldehyde) would serve as a suitable vaccine for the protection of human beings against smallpox.

FROM THE AUTHORS' SUMMARY.

THE GENERALIZED SHWARTZMAN PHENOMENON. K. APITZ, J. Immunol. **29**:255, 1935.

When rabbits are given intravenous injections of certain bacterial culture filtrates at the beginning and at the end of a period of twenty-four hours, death follows within forty-eight hours after the second injection. At autopsy, characteristic changes in the kidneys and a hemorrhagic diathesis are frequently noted. An investigation of certain of the factors involved revealed an almost complete parallelism with those concerned in the hemorrhagic skin reaction (the Shwartzman phenomenon). These findings therefore appear to justify the designation of the reaction described as the generalized Shwartzman phenomenon. Local and generalized Shwartzman reactions represent different localizations of the same type of injury. Additional evidence has been obtained which indicates that a single injection of a potent bacterial filtrate is sufficient to produce regularly a generalized Shwartzman phenomenon in pregnant rabbits.

FROM THE AUTHOR'S SUMMARY.

SCARLET FEVER TOXIN: I. A METHOD OF PURIFICATION AND CONCENTRATION. G. F. DICK and A. K. BOOR, J. Infect. Dis. **57**:164, 1935.

A purified and concentrated scarlatinal toxin containing 20,000,000 or more skin test doses per gram and of low nitrogen content has been prepared by a combination of fractional precipitation with ammonium sulfate, treatment with an aluminum hydroxide preparation, dialysis and evaporation.

FROM THE AUTHORS' SUMMARY.

THE POLYSACCHARIDE CONSTITUENT IN BRUCELLA CELLS. A. D. HERSHEY, I. F. HUDDLESON and R. B. PENNELL, J. Infect. Dis. **57**:183, 1935.

The preparation by Favilli and Biancalani of a specific precipitating polysaccharide fraction from Brucella abortus by prolonged heat extraction was confirmed. From the crude preparation a nonpolysaccharide precipitating substance was separated. A similar precipitating substance was prepared by cleavage from a nonpolysaccharide antigen of Brucella cells. Its relation to the various soluble

specific fractions of Brucella is suggested. The precipitating properties of the polysaccharide prepared according to the method of Favilli and Biancalani appear to be due to a nonpolysaccharide contaminant.

FROM THE AUTHORS' SUMMARY.

DEMONSTRATION OF THE INCREASE OF GLOBULIN IN DIPHTHERIA ANTITOXIN BY THE PRECIPITATION REACTION. G. L. TAYLOR, J. Hyg. **35**:174, 1935.

By titration against horse serum and its protein fractions antihorse serums can be divided into three groups, according to the antibodies responsible for the main or earliest particulating zone, namely, serums containing antibodies against (1) globulin only, (2) albumin only and (3) both globulin and albumin. For the quantitative estimation of a protein fraction in a horse serum it is necessary to use an antiserum containing a main zone antibody acting with that protein only. This is illustrated in experiments designed to show the increased globulin content of diphtheria antitoxin in which antiserums containing antibodies against both globulin and albumin failed to register an increase in the globulin content.

FROM THE AUTHOR'S SUMMARY.

PNEUMOCOCCIC ALLERGY, ANAPHYLAXIS AND IMMUNITY. D. HARLEY, J. Path. & Bact. **41**:491, 1935.

In rabbits there are two types of allergic skin reactions to pneumococci and their products: (*a*) allergy to the SSS, and (*b*) allergy to pneumococcus vaccines. The first named state (*a*) is induced by intravenous injection of a vaccine of virulent pneumococci, is type-specific and is closely related to type-specific immunity and to anaphylaxis to the SSS. The other state (*b*) is induced by intracutaneous injections of vaccines of virulent and avirulent pneumococci alike, and is independent of both type-specific and nucleoprotein antibodies; it is not type-specific, the animals sensitized with one type of pneumococci reacting equally well to the other types and to the Streptococcus viridans vaccines; this type of allergy appears to be of the nature of an increased tissue reaction to the somatic nucleoprotein, and its immunologic function is doubtful.

FROM THE AUTHOR'S SUMMARY.

THE THERMAL RANGE OF GROUP-SPECIFIC ANTISERUMS. F. A. BURÓN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:466, 1935.

Iso-agglutination and absorption of iso-agglutinins were best carried out at icebox temperature, while the optimum temperature for the complement fixation and the so-called amboceptor fixation of Brahn and Schiff with alcoholic extracts of red blood cells was 42 C. The thermal differences may be applied practically in the identification of blood stains.

I. DAVIDSOHN.

BLOOD GROUP PROPERTIES IN THE RABBIT. W. FISCHER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:97, 1935.

Three new iso-agglutinogens, K_3, K_4 and K_5, were demonstrated in addition to the two already known—K_1 (previously A) and K_2 (previously B). Although only 1 of 300 normal serums tested contained an iso-agglutinin, when rabbits are cross-immunized they form iso-agglutinins against the foreign iso-agglutinogens. The agglutinogens K_1 and K_2 determine four groups: O, K_1, K_2 and K_1K_2. Group O is very rare, and the author found it in only 2 of 300 rabbits tested. The agglutinogens K_3 and K_4 are independent of K_1 and K_2 and determine three types of blood: K_3 (13 rabbits), K_4 (36 rabbits) and K_3K_4 (17 rabbits). K_5 is independent of the other four agglutinogens and present in the blood of almost every rabbit. There is no relationship between the presence or absence of human A substances in the organs of rabbits or of preformed anti-A or anti-B substance in the serum and the antigenic structure of the erythrocytes of rabbits. The A

substance of many rabbits is present in the organs and serum but not in the erythrocytes; it is heat-stable and alcohol-soluble. The B_2 substance (Friedenreich and Witt) is demonstrable in organs, erythrocytes and serum; it is heat-stable and alcohol-soluble. K_1 and K_2 are not demonstrable in the organs or serum; they are not very resistant to heat. K_3 and K_5 are found in the organs but not in the serum; they are heat-resistant but apparently not alcohol-soluble. The heteroreceptor for normal species agglutinins for rabbits of human serum is present in the organs, serum and erythrocytes; it is alcohol-soluble and heat-resistant.

A. S. WIENER.

Tumors

A QUANTITATIVE INVESTIGATION OF VITAMIN G IN RAT SARCOMA 39. L. B. BRABEC, Am. J. Cancer **25**:551, 1935.

Quantitative experiments have been made on the occurrence of vitamin G in tissue of rat sarcoma, including a comparison with the vitamin G content of liver tissue from the same animals. The results show considerable difference in the vitamin G content of equal weights of tumor tissue and liver tissue from animals raised on a diet consisting of two-thirds whole wheat and one-third whole milk powder plus sodium chloride to the extent of 2 per cent of the weight of the wheat. The vitamin G content of the tumor tissue was found to be low; the liver tissue was approximately seven times as rich in vitamin G per gram as the tumor tissue. The results were found to be the same whether determined by the average total gain made by the experimental animals in five weeks or in eight weeks. While the liver tissue from animals with growing transplanted tumors appeared to be somewhat poorer in vitamin G than liver tissue from animals without growing tumors, the results of this investigation furnished no evidence that the growing tumor consumed vitamin G in the body of the host. It has also been shown that a diet otherwise adequate but deficient in vitamin G does not prevent the taking or growth of sarcoma 39.

FROM THE AUTHOR'S SUMMARY.

THE RELATIONSHIP BETWEEN VASCULARITY AND THE REACTION TO RADIUM OF SQUAMOUS EPITHELIUM. M. G. SEELIG, C. T. ECKERT and Z. K. COOPER, Am. J. Cancer **25**:585, 1935.

A method is described for compromising the circulation of a portion of the rabbit's ear. The effects produced by irradiation of the tissue with this compromised vascularity are compared with those obtained following similar irradiation of a control normal area. Compromise of the vascularity of the cutaneous epithelium of the ear in this series of rabbits did not alter its radiosensitivity. Radiosensitivity seems to be an inherent quality of the cell, which varies even in individuals of the same species.

FROM THE AUTHORS' SUMMARY.

CARCINOGENESIS IN RATS. A. F. WATSON, Am. J. Cancer **25**:753, 1935.

Tumors can be induced in the skin of the rat, which has hitherto proved resistant to coal tar, by repeated applications of pinene tar mixed with an ether extract of rat tissues. Based on this observation a technic is described by means of which the rat may be used for studies of tar carcinogenesis to supplement those on the mouse. This may prove of value for dietetic or other experiments in which mice are less satisfactory than rats. The histologic appearance of some of the tumors is described. One contained melanin and is apparently the first of this type of tumor induced by tar in the skin of a rat to be recorded. Tumor formation has been induced in rats after as few as three injections of pinene tar agents into the subcutaneous tissues. The medium in which the tar is injected under these conditions may be the deciding factor in determining whether or not tumors are produced.

FROM THE AUTHOR'S SUMMARY.

HISTOLOGIC DIFFERENTIAL DIAGNOSIS OF LYMPHOSARCOMATOUS TUMORS. C. RENNER, Frankfurt. Ztschr. f. Path. **46**:546, 1934.

Renner tries to differentiate between hyperplasia of lymphadenoid tissues, lymphoid leukemic infiltrations and lymphosarcoma. One instance of lymphosarcoma of the tonsils with metastases to the intestines is reported. Round cells with small dark nuclei containing one or two dark bluish-stained nucleoli and thick nuclear membranes were found. There was little variation in the size and shape of the cells. Silver impregnation revealed a minute network of reticular fibers surrounding the tumor cells. Because of the destructive growth Renner rejects the diagnosis of lymphatic hyperplasia. The blood did not show evidence of either acute or chronic leukemia. Immature blood cells were never found. The destructive growth, the slight variation in the size, shape and staining quality of the tumor cells and the mesenchymal stroma are considered characteristic of lymphosarcoma. In a second instance, a reticular cell sarcoma was found involving the mesenteric nodes, the nodes at the hilus of the liver and the retroperitoneal nodes, particularly those situated posterior to the stomach. Many of the tumor cells were polyhedral, but smaller and larger round cells were also seen, and occasionally some that were very large. Some nuclei contained large nucleoli. Many other cells were spindle-shaped. Silver impregnation revealed a dense reticulum. Because of the polymorphous character of the cells, the absence of a blood picture indicating aleukemic leukemia and the destructive growth Renner believes that this is a case of a malignant tumor of the lymph nodes. The variation of the cells and the presence of many reticular fibers make him believe that this is an undifferentiated reticular cell sarcoma.

O. SAPHIR.

SPECIFIC GRANULATION OF THE CHROMAFFIN CELLS OF A PHEOCHROMOCYTOMA. K. SEVKI, Virchows Arch. f. path. Anat. **294**:65, 1934.

An apparently benign encapsulated adrenal tumor the size of an apple was a chance observation at necropsy in a 48 year old man who died of hemorrhage into a cerebral glioma. From histologic examination it was not possible to determine whether the tumor was of cortical or medullary origin. Chromaffin and other epinephrine reactions failed because the material had not been properly fixed for such procedures. A slight modification of the Giemsa staining method, which is described, revealed the presence of cells with characteristic eosinophilous granulation. Use of this method in the study of normal adrenal glands from human beings of various ages and from various species of animals established that oxyphil cells are characteristic of the adrenal medulla. The method appears to be of value in determining the chromaffin orgin of tumors when other procedures fail.

O. T. SCHULTZ.

LYMPHADENOSIS OF THE BONE MARROW. A. F. ZANATY, Virchows Arch. f. path. Anat. **294**:80, 1934.

To a previously reported case of what Zanaty terms primary medullary lymphadenosis (abstr., Arch. Path. **19**:885, 1935), he adds two further cases, both occurring in girls aged 4 years. In these, as in the previous case, the condition ran an aleukemic course, and the predominating clinical feature was anemia. He believes that it is necessary to recognize as a special form of lymphadenosis or leukemia a form characterized clinically by early anemia. In this respect it is like myeloid leukemia, in which anemia is an early manifestation, in contrast to the usual form of lymphoid leukemia, in which anemia is a relatively late manifestation. Anatomically the condition under consideration is characterized by replacement of the bone marrow by proliferating lymphoid tissue. He derives the hyperplastic tissue from indifferent mesenchymal stem cells of the marrow, with differentiation of the tissue into lymphocytes. He accepts the unitarian doctrine of the origin of both myeloid and lymphoid cells in the bone marrow, at least under pathologic conditions, from an indifferent stem cell.

O. T. SCHULTZ.

MYOBLASTIC SARCOMA OF THE PULMONARY ARTERY. H. KUDLICH and W. SCHUH, Virchows Arch. f. path. Anat. **294**:113, 1934.

To the rare tumors of the heart and large vessels the authors add a myoblastic sarcoma of the pulmonary artery. They could find references to only three previously reported tumors of this vessel. Their tumor involved the pulmonic valve, grew into the artery in thrombotic fashion, invaded the tissue at the root of the lung and metastasized to the adrenal gland. They incline to the view that the neoplasm had its origin at the valve and grew along the vessel, although they cannot exclude the possibility that it sprang from the artery rather than from the valve.

O. T. SCHULTZ.

CHANGES IN THE BUCCAL MUCOSA FOLLOWING IRRADIATION. J. BORAK, Virchows Arch. f. path. Anat. **294**:304, 1934.

When neoplasms of the buccal cavity are irradiated changes occur in the adjacent mucosa that vary with the situation of the latter. The mucosa of the gum, soft palate and uvula reacts successively by hyperemia, edema and inflammation with cellular infiltration and deposition of fibrin. The epithelium disappears by lysis and necrosis. In the mucosa of the tongue and hard palate such vascular reactions do not occur. Leukoplakic areas appear, due to hyperkeratosis of the epithelium. Later the patches become yellowish and finally disappear, the epithelium having been lost by desquamation. These varying reactions are important in estimating the adequacy of irradiation of buccal neoplasms. It must cause destruction of the tumor cells. Such destruction does not occur unless the application has been sufficient to cause loss of epithelium of the adjacent mucosa. Leukoplakic hyperkeratosis is not an indication for cessation but rather for continuance of irradiation, since desquamation of the hyperkeratotic epithelium must be brought about.

O. T. SCHULTZ.

CUTANEOUS METASTASES IN THE FIELD OF IRRADIATION OF A PYLORIC CANCER. O. SCHÜRCH, Ztschr. f. Krebsforsch. **41**:47, 1934.

There is described a case of pyloric carcinoma in which after operation (without excision) and prophylactic irradiation early cutaneous metastases appeared which were limited to the irradiated area. The phenomenon is directly the opposite of what would be expected from experimental observations. Schürch explains it on the ground of vascular trauma by the irradiation, with establishment of a site of lowered local resistance to tumor implantation.

H. E. EGGERS.

Technical

THE PRESERVATION OF BACTERIA BY DRYING IN VACUO. E. LEIFSON, Am. J. Hyg. **23**: 231, 1936.

The advantages of a simple and reliable drying technic for the preservation of bacteria are many. Much of the work and expense of transferring stock cultures are eliminated. The changes which take place in the dried cultures are probably less than in similar cultures kept on ordinary laboratory mediums. Considerably more work needs to be done, however, on variations undergone by bacteria in dried cultures before any definite statement can be made on this subject. In the light of the work that has been done on drying it seems a good practice in bacteriologic laboratories to dry all freshly isolated or new cultures which are intended for future use. Dried cultures may be shipped to distant places with greater ease and with less danger of killing them than active cultures.

FROM THE AUTHOR'S SUMMARY.

A Stain for Neuroglia in Formaldehyde-Fixed Paraffin Sections. Cobb Pilcher and Elizabeth Owings, Arch. Neurol. & Psychiat. **35**:351, 1936.

The authors recommend a modification of the Bielschowsky silver method for staining gliomas and other tumors that have been in formaldehyde solution for as long as ten years. Blocks are embedded in paraffin, and sections are cut 11 microns thick, mounted on slides with glycerin-albumin mixture and after the removal of paraffin and washing in distilled water are stained for forty-eight hours in a 2 per cent solution of silver nitrate (in the dark). The rest of the procedure is practically the same as in the classic method. The authors do not consider the stain specific, as connective tissue, ganglion cells, nerve fibers and neuroglia are impregnated equally well. Primitive or immature glia cells (glioblasts) are well shown, but oligodendroglia and microglia are stained poorly.

George B. Hassin.

Mediums for the Cultivation of Tubercle Bacilli from Sputum. S. R. Jamieson, J. Path. & Bact. **42**: 435, 1936.

Six mediums have been compared as to their value in the cultivation of tubercle bacilli from sputum following preliminary treatment of the organisms with 6 per cent sulfuric acid according to a slightly modified Corper-Uyei method. The medium of Petragnani gave the best results, being superior to the microscopic method as regards the number of positive results, while producing the earliest possible growth. Because of the simplicity of its preparation and the excellence of the results obtained, this medium is particularly recommended for the primary cultivation of tubercle bacilli following the treatment with sulfuric acid. The medium of Löwenstein is also recommended, as it yielded results almost as good as those of the Petragnani medium. These two mediums were superior to the other four with regard to the number of positive results obtained. The mediums of Herrold and Corper-Uyei also gave very good results, but greater care was necessary in their preparation. These four mediums, therefore, all gave reliable results, and any one of them may be used with confidence in the routine isolation of tubercle bacilli from sputum. The mediums of Petroff and Sweany-Evanoff, owing to frequency of contamination and tardiness of growth, were inferior to the other four. In this series the use of culture mediums has proved itself superior to direct microscopic examination. Of the 100 specimens examined, only 92 gave positive results by the microscopic method as against 100 positive results given by the two best culture methods. A comparison with guinea-pig inoculation was not carried out in this investigation, but the positive cultural findings in 8 specimens with no tubercle bacilli demonstrable microscopically and in 5 others in which they were very scantily present suggest that the culture method will give as good results as guinea-pig inoculation, besides being cheaper, quicker and less fallacious.

From the Author's Summary.

The Müller Conglobation Reaction No. 2 in Spinal Fluids. T. M. Vogelsang, Acta dermat.-venereol. **16**: 37, 1935.

The Müller conglobation reaction no. 2 for spinal fluid and for serum is simple and is quickly performed. The result may be read at the end of three hours and is little dependent on the personal judgment of the investigator. In the case of spinal fluid this reaction appears to be as sensitive and specific a test as the Bordet-Wassermann reaction.

From the Author's Conclusions.

Society Transactions

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, March 28, 1936

KORNEL TERPLAN, *President*

WILLIAM F. JACOBS, *Secretary*

AIR EMBOLISM WITH UNUSUAL SOURCES AND PATHOLOGIC FEATURES. K. L. TERPLAN and E. MILCH.

In the last year four fatal cases of air embolism were observed. In one the condition followed pulmonary lobectomy and showed the usual clinical features, including especially convulsions. Post mortem no air was seen in the left side of the heart or in the cerebral arteries. However, histologic examination of the brain revealed scattered areas of ischemic necrosis of nerve cells, most prominent in the third layer of the cerebral cortex. As regards the other three cases, either the mechanism which brought about the entrance of air into the venous circulation or the gross anatomic observations post mortem are of such interest that a brief discussion of each case seems justified.

CASE 1.—A 31 year old white woman who had been married for three years was to be tested for sterility by determination of the patency of the tubes. First, the rather rigid cervix was gradually dilated. Then the Rubin artificial tubal insufflation showed that both tubes were patent. Following the insufflation the cervix was further dilated until a small curet could be passed; no membrane was recovered, however. (The patient had just completed menstruating; this information she had refused to give on admission.) Immediately following the operation, before she had been removed from the operating table, the pulse volume fell rapidly; the rate was 54. The blood pressure fell to 70 systolic and 48 diastolic. Respiration was deep and slow. In spite of all supportive measures, the patient died within a few minutes.

At postmortem examination one-half hour later, the body showed marked cyanosis of the face, neck, conjunctivae and lips. The pericardial sac was distended by the voluminous right side of the heart. (The sac was then filled with water by the prosector.) The right ventricle was opened, and there escaped continuously many air bubbles with little fluid blood. The right atrium and the superior and inferior venae cavae were distended by fluid blood only. The pulmonary artery, however, contained only froth, with practically no fluid blood. Although the foramen ovale was open, there was very little fluid blood in the left atrium. The left ventricle was empty and contracted. The lungs showed very marked acute emphysema.

In this case some portion of the injected air had passed from the cavum uteri through the patent tubes into the peritoneal cavity. The remaining air was sufficient in quantity to bring about sudden tamponade of the pulmonary artery and the right ventricle by entering small endometrial veins which were opened by the curet. The position of the patient during the operation, with the pelvis raised, may have facilitated the aspiration of air into the endometrial veins.

CASE 2.—A 43 year old woman suffered from inoperable carcinoma of the cervix with severe pain in the lower part of the abdomen. Cordotomy for relief of the pain was done under narcosis obtained with tribromethanol in amylene hydrate. The patient was kept in a sitting position. The spinal processes and laminae of the seventh cervical and first dorsal vertebrae were removed piece-

meal. When the dura was exposed the patient took a few gasping respirations and ceased breathing. Coincident with each respiration there was a distinct sucking sound in the wound. With administration of oxygen and carbon dioxide respirations were resumed but irregularly. Following incision of the dura they ceased. Stimulants and artificial respiration failed to revive the patient.

The postmortem observations differ from those in case 1 in the marked distention of both jugular veins and of the innominate vein by huge air bubbles. The right atrium, too, was markedly distended, more than the right ventricle. Both of these and the pulmonary artery contained foamy blood and a few very thin blood clots covered with air bubbles. (In this case the postmortem examination was performed six hours after death.) The left ventricle was entirely empty and contracted.

In this instance the air apparently entered directly the inner vertebral venous plexus outside of the spinal dura; the veins had been opened by the removal of the laminae. The sitting position of the patient also may have played a part in the suction of air into the venous plexus.

CASE 3.—A 2 year old white girl known to have been suffering from congenital heart disease became severely ill with pneumonia, hemorrhagic pleuritis and erysipelas. The general condition of the child was very poor. After an intravenous drip of 5 per cent dextrose solution had been concluded, the child died suddenly. The attending pediatrician expected an embolic cause for the sudden death.

In this case all the air was trapped completely in the main stem of the pulmonary artery, which contained typical pinkish white foam but neither fluid blood nor clots. There was a distinct fusiform distention of the main stem of the pulmonary artery. The right ventricle and the right atrium contained only fluid blood and a few thin clots. (The postmortem examination was performed about seven hours after death.) In the major branches of the pulmonary artery there was mostly fluid blood with hardly any foam.

An apparently small amount of air had sufficed to bring about immediate death in a child suffering from effusion in the left pleural cavity, marked pressure atelectasis and diffuse bronchopneumonia of the right lung.

Comment.—All three cases illustrate the major importance of the foam formation in the main stem of the pulmonary artery. Not merely for reasons of diagnosis but also in order to understand the effect of air embolism on the heart and general circulation, it is necessary to observe carefully the size, distention and dilatation of the different chambers of the right side of the heart and the amount of air, foam and fluid blood in these chambers, especially in the pulmonary artery proper. The left side of the heart also should always be carefully searched for gaseous or fluid content. In case 3 the absence of foam or air from the right ventricle was very impressive. It seemed as if the foam by its tension in the stem of the pulmonary artery had prevented any further flow of blood from the ventricle into the pulmonary artery.

FURTHER STUDIES ON PNEUMONIA IN NEW-BORN INFANTS. MARGARET WARWICK.

Of 430 consecutive babies examined post mortem who were stillborn or who had died within the first ten days of life, thirty-two, or 7.5 per cent, were too macerated for detailed examination, but, of the remaining 388, seventy-seven, or 19.8 per cent, showed pneumonia. Of these, thirty-seven, or 48 per cent, lived less than twenty-four hours, and fifty-four, or 70 per cent, lived less than forty-eight hours, showing that the condition was closely related to birth. All of the lungs were stained for bacteria, which were present in twenty-two, or 29 per cent. The percentage increased with age (37), and among those living less than twenty-four hours only three, or 8 per cent, showed bacteria, suggesting that the bacteria might be introduced after birth by artificial respiration or by aspiration. The possibility of bacteria having been introduced after premature rupture of the membranes was excluded by the fact that forty-nine, or 63 per cent, of the infants

had had the membranes ruptured less than ten hours before birth, and fifty-six, or 73 per cent, had had them ruptured less than twenty-four hours before.

The majority of these infants had had difficult births, for only seventeen, or 22 per cent, had been born by spontaneous delivery, and, of these, five had been born after unusually long labors. Only eleven, or 14 per cent, were recorded as "good" at birth, and forty-nine, or 63 per cent, were dead or "poor," and the rest were "fair." Of the seventy-seven, only sixteen died without other pathologic lesions, such as malformations or birth injuries, sufficient to have caused death without the pneumonia. Therefore, the pneumonia seems to be associated with the process of birth.

Frequently an infant may have premature respirations before or during birth due to asphyxia from some disturbance of the circulation of either the mother or the child. In this way amniotic fluid, containing cornified epithelial cells and often bile pigments from meconium, is aspirated deep into the lungs. Of the seventy-seven cases of pneumonia, in sixty-five, or 84 per cent, cornified epithelial cells and bile pigment were present, while in the remaining twelve, or 18 per cent, the pus cells were numerous enough to have obscured the evidence. So it seems that these irritating substances, which are foreign bodies, may set up an inflammatory process identical with a "chemical" pneumonia, which would not have a toxic effect but would mechanically fill the alveoli and prevent proper aeration. An infant would probably have premature respirations during a long and difficult delivery, and if it were born in a poor condition it would lack the energy and vitality to expel the amniotic fluid, so that much would remain to cause pneumonia. A few may have pneumonia already established at birth if they have breathed long before.

Therefore, it seems that the pneumonia which is found in about one-fifth of all infants dying during the first ten days of life is the effect of a hazardous birth and not an infectious process, and is more commonly found in weak infants or in those who have been badly maltreated during birth.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, April 23, 1936

N. Chandler Foot, *President*

Milton Helpern, *Secretary*

Dermoid Cyst of the Ovary with Squamous Cell Carcinoma. L. H. Meeker.

Cystic teratoma of the ovary is generally considered to be benign, but malignant changes do occur. Primary epidermoid carcinoma in a dermoid cyst is, however, extremely rare. Ewing cites the compilation by Bab, who in 1932 collected thirty-seven examples. Counsellor and Wellbrock (*Am. J. Obst. & Gynec.* **28**:40, 1934) were able to find thirty-nine authentic cases recorded in the literature, and added four cases from the Mayo Clinic, making a total of forty-three proved cases. Their survey stated that epidermoid carcinoma occurred in 1.7 per cent of dermoid cysts of the ovary. The youngest patient was 40 and the oldest 67 years.

The patient in the present instance was 71 years of age. The chief complaint was pain in the lower part of the abdomen and intestinal disturbance. She was married and had one child. There had been no vaginal bleeding since the menopause, twenty years before. An abdominal mass without definite outline was palpated. Operation disclosed a dermoid cyst of the right ovary. It was adherent to the mesentery and mesosigmoid and had perforated into the intestine. Death occurred from postoperative pneumonia.

The gross specimen was a cystic mass 90 mm. in diameter. The cyst contained fat and abundant hair, and the wall varied in thickness from a few millimeters to 25 mm. The thickest portion was made up of firm, grayish-white tissue, and here the outer surface had been cut away from the adherent intestine.

Sections through the thickened portion of the wall showed a dense fibrous stroma infiltrated by nests and strands of stratified squamous epithelium. Many of the epithelial cells lined alveolar cystic spaces. The stroma was continuous with the wall of the fallopian tube and the attached intestine. The neoplastic epithelium, showing degenerative changes, invaded both structures, encroaching on the mucosa, and caused the perforation of the intestine.

The nests and strands of invading cells were mature squamous epithelium; there was an occasional suggestion of pearl formation, and mitotic figures were fairly common. There was lymphocytic infiltration about the epithelium in many areas. No appendages other than hair were associated with the epidermoid lining of the cyst.

This squamous cell carcinoma in the ovary was a primary carcinoma of the dermoid cyst.

To the collected cases from the Mayo Clinic should be added four cases recently reported—two by Petrowa and Karaewa, one by Szathmary and one by Fein. These four with the case now reported make a total of forty-eight cases of dermoid cyst of the ovary with primary squamous cell carcinoma.

Oophoroma Folliculare (Brenner) of the Ovaries. L. H. Meeker.

The patient was 42 years of age. Her chief complaints were metrorrhagia and menorrhagia of two months' duration. She was married and had three children, the youngest 20 years old. She had had no miscarriages. At operation the uterus and adnexa were removed.

The gross specimen disclosed multiple uterine fibroma. One pedunculated fibroid measured 20 mm. and another 70 mm. in diameter. The largest intramural tumor was 60 mm. in diameter. The oviducts were similar and not grossly pathologic. The ovaries were similar and approximately of equal size, 36 by 22 by 15 mm. The cut surfaces of both presented what appeared to be numerous large corpora albicantia.

It was these white areas that on microscopic examination revealed an unusual picture. They were composed of nests of large polyhedral cells with a basal layer of small cells with dark nuclei. Some of the nests contained lumens lined by columnar epithelium with cilia. Some of these were filled with colloid or mucinous exudate, others with exfoliated epithelium and still others with calcific bodies. The general picture was that of regularly arranged, orderly cell nests with little variation in the general cell type. Some of the nests were connected with strands of cells extending from the surface of the ovary. About the nests the stroma varied from the usual ovarian type to packed and twisted bundles of fibroblasts.

Brenner called this type of tumor "oophoroma folliculare." Whether one is dealing with a benign or a malignant new growth is a disputed question. Plaut suggested the designation "fibro-epithelioma mucinosum benignum." Bland and Goldstein concluded that tumors of this type are "rather malignant."

The striking structure of these tumors makes them easy of identification, notably the tendency to the formation of small cysts lined by cylindric epithelium and the mucinous content.

The very recent compilation of reports on ovarian tumors by Bland and Goldstein includes reports of sixty-six tumors of the Brenner type. The tumor which I have described was bilateral and was an example of the solid form of oophoroma folliculare. It conformed to Plaut's so-called "fibroepithelioma mucinosum benignum."

DISCUSSION

Alfred Plaut: I should like to ask whether the whitish areas of the cut surface which looked like corpora albicantia at first still looked like corpora albi-

cantia after the diagnosis was known, or whether details could then be seen in them. I had the impression from the lantern slide that some of them contained dots, probably corresponding to the cavities within the epithelial portions. I have never seen cilia in the small cavities inside the solid masses. I should like to know on what findings the authors mentioned based their opinion that these tumors may be malignant. I should like to take a little exception to keeping up the old name "oophoroma." The tumor has nothing to do with ova, as everybody knows, and why it should be called "oophoroma" I cannot see.

L. H. MEEKER: My colleagues and I have kept the name used by Brenner because the name suggested by Dr. Plaut, although we highly approve it, includes the word "benign," and that did not seem fair to those who believe that they have demonstrated that tumors of this type are malignant. Bland and Goldstein concluded that both sides of the question should be considered. Cilia have been mentioned, if I am not mistaken.

A CASE OF MYOSARCOMA OF THE STOMACH WITH FATAL HEMORRHAGE. A. J. FRIED (by invitation).

A 37 year old white man gave a history of profuse bleeding after extractions of teeth. Five days before admission there was excruciating pain in the upper part of the abdomen and vomiting. After a second administration of a cathartic the pain became worse, and the patient collapsed and died.

At necropsy there was 1,500 cc. of fluid blood in the abdomen. The greater part of the stomach was covered by a friable clot, in which a pedunculated roughly globular tumor measuring 5 by 3 cm. was embedded. The tumor was attached to the anterior gastric wall in the pyloric region below the lesser curvature. It was firm and elastic. The cut surface was grayish yellow, smooth and glistening, and had a wide, thin-walled blood vessel ending abruptly at the periphery. This was apparently the source of the hemorrhage. The wall of the stomach was not infiltrated, but two circumscribed firm nodules were palpated at the base of the pedicle in the subserosa.

The microscopic picture was the same throughout, with oval, round and polyhedral cells, containing from round to sausage-shaped vesicular nuclei. Occasional giant cells were seen. Mitotic figures were not recognized. The nodules in the subserosa were largely encapsulated except where they extended outward through the muscularis. Here normal smooth muscle bundles extended into the neoplastic tissue, where they gradually lost their identity. The overlying mucosa and muscularis mucosae were not involved.

DISCUSSION

N. CHANDLER FOOT: Leiomyosarcoma of the stomach is probably a great deal more frequent than any one thinks. It has been my experience to see four instances, all intramural, the neoplasms varying all the way from dedifferentiated primitive types with extensive metastases to one particular tumor which was well differentiated and about which there was some question as to its being a sarcoma or not. Although there are already a good many cases of this type recorded in the literature, I believe a great many more occur that are not recorded. Pathologists should report them more frequently.

ANAPLASTIC CARCINOMA OF THE MAJOR VESTIBULAR (BARTHOLIN'S) GLAND. S. M. RABSON and L. H. MEEKER.

Malignant disease of Bartholin's (the major vestibular) gland is rare and not often considered in the differential diagnosis of diseases of this organ. Two cases of carcinoma are described:

1. Anaplastic adenocarcinoma was seen in a 33 year old woman whose condition was diagnosed as Bartholin's cyst about three months before resection of the tumor. Radiation therapy was employed, but metastases developed, and the patient died ten months after the removal of the primary neoplasm. At necropsy there

was no evidence of recurrence at the primary site in the left labium majus. Metastases were found in the brain, dura, lungs, heart, liver, pancreas, adrenal glands, kidneys, left ovary and mediastinal lymph nodes, all showing a picture similar to that of the primary tumor.

2. A 53 year old woman noted the development of a mass in the left labium majus about four months before admission to the hospital. Resection of a transitional cell carcinoma was performed. Death took place less than six months later. There was no necropsy.

In the first patient's tumor normal acini and ducts of Bartholin's gland were still present, in part intact and in part replaced by the anaplastic adenocarcinoma. Here all of Honan's criteria are satisfied: (1) a typical site in the labium; (2) a position deep in the labium; (3) a connection with the duct; (4) the presence of intact normal tissue.

In the second patient's new growth no normal elements were found, nor was there any evidence of connection with the ducts. The similarity, however, between the transitional epithelium seen in the ducts in routine surgical specimens and the transitional cells of the neoplasm justify the diagnosis of Bartholin gland carcinoma.

Fifty-six published or recorded cases of carcinoma of Bartholin's gland have been collected. At the New York Post-Graduate Medical School and Hospital 1.1 per cent of all lesions of this gland are reported as carcinoma—figures generally similar to those reported from the Mayo Clinic (from 0.8 to 0.9 per cent). The youngest patient was 19 years old, and three were in the eighth decade of life. A vulval mass is the most frequent symptom. Resection and radiotherapy employed together offer the longest postoperative period of freedom from symptoms.

DISCUSSION

PAUL KLEMPERER: Will Dr. Rabson and Dr. Meeker clear up my mind on one point: Is the differentiation of carcinoma of this gland from adenoma or carcinoma of the sweat gland always possible? The location of the tumor would make this sometimes difficult. I have never seen a carcinoma of Bartholin's gland; I have seen one carcinoma and two benign tumors of sweat glands in the vulva. I wonder if it is possible to differentiate these tumors on histologic grounds.

ALFRED PLAUT: I had a similar question in mind. I, too, never had the opportunity of seeing a carcinoma of Bartholin's gland. I have seen several examples of benign hidradenoma of the vulva, as Pick called it, and I have seen two or there examples of intracystic tumor of the region of Bartholin's gland, which gave me a little difficulty before I decided to call them nonmalignant or borderline. I was able to follow only one of the patients; in that patient there was no recurrence. I wonder if Dr. Rabson and Dr. Meeker, in studying the literature on carcinoma of Bartholin's gland, have come across any references to these rather wild-looking intracystic papillary but obviously benign tumors.

S. M. RABSON: In reply to Dr. Plaut: In going through the literature we did discover certain cases of distinctly benign adenoma. These have even been reported in some compilations in the literature as carcinoma, but on careful reading we concluded that the matter concerned adenoma. Some of the cases of adenocarcinoma are recorded as being of the papillary type. We have come across no reference to a benign papillary adenomatous condition.

In response to the question of Dr. Klemperer we may say that the neoplasm stands out readily from the surrounding structures. So characteristic is its location that it is generally diagnosed as an infection or a cyst of Bartholin's gland. Furthermore, the tumor is always found beneath the capsule of Bartholin's gland, or it extends into the tissue underlying the capsule, which is compact connective tissue and some muscle. Most of the extensions were downward and inward rather than along the surface, where one would expect to find a tumor of the sweat glands. Dr. Healy's tumors had been diagnosed histologically by Dr. Ewing.

COR TRILOCULARE BIVENTRICULARE WITH DEXTROPOSITION OF THE AORTA AND PULMONIC STENOSIS. L. H. MEEKER and M. M. MALINER (by invitation).

The heart is that of a boy 10 months old, the son of Italian parents. He had been blue since birth. There was a history of attacks of general spasticity, failure to take food and irritability. He was now markedly cyanotic and dyspneic with clubbing of the fingers and toes. When admitted to the hospital he was semi-comatose. Examination disclosed a heart markedly enlarged to the right, a loud sternal murmur, tachycardia and an enlarged liver. The left palpebral fissure was much elongated.

Death was due to bronchopneumonia. At necropsy the left lung had three lobes and the spleen was lacking. The heart weighed 57 Gm. and was markedly enlarged in all chambers. The great vessels were transposed. There was a common auricle, partly divided by a narrow crescentic septum with persistent ostium primum. The venae cavae opened into it in the normal position. The common auricle opened into both ventricles, overriding the wide ventricular septal defect. The ventricles were guarded by a common valve having four segments. The anterior leaf of the valve was divided into two segments, which passed over the upper free border of the ventricular septum from the left to the right ventricle and were attached to the wall of the right ventricle. The third segment was similarly attached and was fenestrated and nodular. The fourth segment was not unusual.

The ventricular septum had a wide basal defect and a second defect, which was a cleft 1 cm. long in the anterior part of the septum.

The right ventricle was much smaller than the left, but the walls of both were hypertrophied.

The aorta arose from the right ventricle, was hypertrophied, and its opening was guarded by three semilunar cusps. The pulmonary artery was stenosed and guarded by two fused cusps. Above the cusps the artery was dilated to its bifurcation, the left branch giving off the ductus arteriosus, which was slightly patent.

DISCUSSION

MAUDE ABBOTT (by invitation): At first sight this specimen seems confusing, but after hearing the elaborate and careful discussion of it, I find that the anomaly is clear in most particulars. I had the privilege of going over this case carefully, and I remain puzzled on at least one and possibly two points. The first is the relation of this rarity, which the authors have been calling the "persistent right reptilian aorta," to the pulmonary artery, and the other is the remarkable second interventricular septal defect. I myself and I am sure every one must have been struck in looking at the second and then the third drawing by the fact that one has here a conjunction of two types of interventricular septal defect. There is a defect along the whole base of the interventricular septum; there is an incomplete septum in its upper part, and then one notices the probe going in behind the anterior segment of the mitral valve, passing into the right ventricle at some distance below the base of the incomplete interventricular septum. This second defect is separated from the free base of the interventricular septum above by 0.5 cm. of muscular tissue, and it has healthy muscular borders around it. It is evidently a bulbar septal defect, that is, a septal defect which is situated in the anterior or aortic septum, and any one who is familiar with the heart of the turtle will recognize that there one may see a similar condition. If one looks at the dorsal surface of either this malformed heart or the heart of the turtle one sees that the ventricles are not as yet divided into two lateral cavities, but that there is a ventral and a dorsal ventricle, the latter of which has two corners, into which the two auriculoventricular orifices open, one on either side, and that on the right side there is a large triangular bulbar septal defect, through which the right corner of the dorsal ventricle communicates with the ventral ventricle, which gives off the pulmonary artery. These features are even more marked in the turtle, and I think in the heart demonstrated one has a beautiful example of a

condition which one does not see clearly in the embryo, that is, the period of development in which two defects exist, the bulbar septal defect and the communication with each side of the dorsal ventricle as seen in the plate. The coexistence of these defects in the embryonic heart has been quite clearly brought out by Fraser of London and others who have studied the subject, and it is beautifully shown here. The point that seems to me to bear on Spitzer's theory is this: that this second septal defect opening into the conus of the right ventricle has a muscular border which definitely separates it from the opening of the pulmonary artery on the one side and which itself lies behind and to the left of the arch formed by the crista supraventricularis anteriorly; and that in front of this again is this large "right" aorta, separated from the mouth of the obliterated "left" aorta on the other side of the heart by the defective septum. In other words, one has two incomplete septums; one sees one incomplete septum separating the pulmonary artery from this bulbar septal defect, and one sees another one separating the latter from the large "right" aorta. To me this is interesting, and I hope that Dr. Meeker will succeed in sending this heart to Professor Spitzer, if he is still in Vienna, to see what he thinks of it. On the one hand, it may throw light on his theory of persistent reptilian aorta; on the other, it may confuse certain points, because, if this suggestion I have made is not right, that is, if this defect does not indicate the orifice of the left aorta that lies behind it, it may indicate that here one does not deal with a persistent right reptilian aorta but with the dextroposed human aorta and that a persistent right reptilian aorta does not occur in the malformed heart.

CHICAGO PATHOLOGICAL SOCIETY

CARL APFELBACH, *Vice-President, in the Chair*

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HISTOLOGY OF DENTAL INFECTIONS. RUDOLF KRONFELD.

Earlier studies of dental infections were made by bacteriologic methods or by histologic examination of biopsy specimens of dental tissues. Much can be learned from a study of sections of large pieces cut from jaws of human cadavers containing diseased teeth in various stages of periapical infection. In such preparations the topographic relationship of granulomas and root end cysts to the bone, maxillary sinus and other structures can be studied. A comparison between roentgenograms taken before decalcification of the jaw specimens and the histologic sections through the corresponding fields reveals important correlations between clinical diagnosis and tissue changes.

DISCUSSION

J. P. SIMONDS: This is an excellent demonstration of pathologic conditions about the roots of diseased teeth.

EFFECT OF IMMUNE SERUM ON TRANSPLANTABLE FLEXNER-JOBLING RAT CARCINOMA. BERNARD PORTIS and HAROLD ROTH.

Chemical analyses of cancer tissue reveal proteins which vary only little from those of the normal tissues in which the growths arise. However, the demonstration of important variations from normal is beyond chemical methods. Hence, it seemed advisable to study immunologically the specificity of the proteins in cancers and, if such proteins were found to be specific, to study the effect of immune serum on cancer tissues in vivo.

The tumor used was found by Flexner and Jobling in a rat in 1906 as a spontaneous growth, about the size of a walnut, attached to the left seminal vesicle. It was firm, and there were no metastases. It was a vascular mixed carcinoma and sarcoma, consisting of polymorphous cells rich in protoplasm with single or multiple vesicular nuclei and of elongated and spindle-shaped cells with solid nuclei. Transplants grew readily in rats, and for the first four generations metastases were produced by transportation of the cancerous cells in the blood stream as in sarcoma and by the lymph stream as in carcinoma. After the fifth generation, however, lymphatic metastasis became dominant and has continued dominant in the succeeding years; this is characteristic of carcinoma. The adenocarcinomatous structure also became progressively more established. The tumor is highly invasive, and its growth is not interrupted by muscle, fascia, bone or cartilage.

The results of experiments with anticancer serum differ greatly. There are two diametrically opposed views. Jensen, twenty-five years ago, treated mouse carcinoma with immune serum prepared in rabbits but was unable to influence its growth in mice. Borrel also was unsuccessful with immune serums prepared in sheep and fowl. In a critical analysis Woglom concluded that immunity to cancer cannot be conferred by any tissue or body fluid. Lumsden concluded that an antiserum for Jensen rat sarcoma was highly effective if kept in close contact with the tumor. He noted that the antiserum was lethal in cultures of cancer tissue. In later reports he stated that the euglobulin fraction of the antiserum was the main and perhaps the only fraction that contained the antibodies. Recently he reported that the euglobulin fraction could be purified and made more stable by adsorption with aluminum hydroxide and drying over phosphorus pentoxide. In a study of human cancer Herzfield found complement-fixing antibodies in the serum of from 50 to 60 per cent of patients with internal carcinoma; in the serum of 5 per cent he noted nonspecific reactions. Saphir and Hirschberg observed a positive reaction in the serum of 77.7 per cent. Zakrzewski and Fuchs concluded that these and other immunologic tests were not specific because the biologic reactions were obscure in the presence of neoplastic tissue.

The original rats with Flexner-Jobling carcinoma were secured from the Crocker Institute. The tumors were removed aseptically, and small fragments were injected subcutaneously into other rats. The range of tumor takes was from 80 to 90 per cent. Each growth attained the size of a hickory nut in about three weeks, the most suitable time for experimentation. Tumors of this size were removed from the rats, carefully triturated, and salt solution added. Rabbits were used for preparing antiserum. The suspension was injected into the peritoneum of the rabbit, four injections being made at intervals of one week. One week after the last injection the animal was bled and the serum separated. Normal rat muscle and rat liver also were used as antigens in the preparation of antiserum. This and normal rabbit serum served as controls in the experiments. Rats with tumors were separated in cages, and the tumors were charted. The rabbit antiserums were antirat carcinoma, antirat liver and antirat muscle. The experiments were controlled with normal rabbit serum and with untreated rats that carried carcinoma transplants. Four injections of antiserum and of control normal serum in amounts of 0.5 cc. were given during three weeks. The injections were made into the tumor in one group and subcutaneously in another. The size and shape of the growths were charted weekly for several months. The second part of this experiment consisted in fractioning the immune serums and using the euglobulin fraction.

The antirat carcinoma serum definitely retarded growth of the carcinoma transplants when it was injected into the transplants but had little effect when injected subcutaneously. The antirat liver and antirat muscle serums and the normal rabbit serum had no obvious effects. These encouraging results were nullified in further experiments by the occurrence of fatal anaphylaxis. This complication appeared with such regularity that the experiments were stopped. The same condition occurred with the euglobulin fraction. Hence, there are no positive conclusions.

The experiments suggest, however, that immune serum may be produced in rabbits with rat carcinoma as an antigen and that the protein constituents of rat carcinoma are different from those of the normal tissues of the animal.

This work has been aided by a grant from the Committee of Scientific Research of the American Medical Association.

METEOROLOGICAL ASSOCIATIONS OF ENDOCARDITIS. W. F. PETERSEN.

Endocarditis as a disease of northern latitude, a priori, may be related to several associated phenomena, namely, the more frequent penetration of flora from the upper respiratory and gastro-intestinal tracts into the blood stream, the physiologic association of the pressor episode with the polar infall and the undue biologic stimulation which ensues for the inhabitant of northern latitudes in the winter and spring when, with undue environmental demand and the exhaustion of buffers, vitamins, etc., the vessels and cellular interfaces in general become unduly permeable.

Under such conditions an undue increase in the blood pressure with its mechanical stimulation of the valvular contact surface at a time when the organism is unduly acid, with bacteria circulating, presumably may be followed by bacterial localization.

In a series of clinical cases in which definite dating of the beginning of endocarditis was made possible because of the association with dental extraction the influence of untoward meteorological conditions was demonstrated, and the association of periods of increased blood pressure as a factor conditioning the valves for bacterial localization was shown to be probable. Later clinical episodes observed during the course of the endocarditis were associated with meteorological alterations, and the death of the patients followed periods of greater cardiac demand incidental to polar episodes.

DISCUSSION

S. A. LEVINSON: Acute endocarditis following extraction of teeth has been recorded in several instances at the coroner's office. An investigation revealed that in these instances the condition was associated with meteorological disturbances.

THE PRESSOR EPISODE AND ITS RELATION TO EXPERIMENTAL ENDOCARDITIS IN DOGS. A. J. NEDZEL.

R. H. Jaffé has stated that histologic evidence indicates that bacteria localizing on the heart valves do not come from within the valve but from the blood stream. He also stated that their adherence to the valve is not primarily a matter of thrombus formation but due to changes of the endocardium. Examining valves from early cases of bacterial endocarditis, he observed a thickening of the endothelium, and he stressed the palisade of the reticulo-endothelial cells from the subendocardium as forming an adhesive surface.

There is a seasonal tide in the onset of endocarditis and of its exacerbations. At this particular time the organism makes the greatest efforts to adapt itself to the shifting cyclonic circulation of the atmosphere. This adaptation is manifested in changes of the pressor relations of the vascular system, which lead to stimulation of the valves already stimulated (on account of anatomic location and physiologic rôle), especially the mitral valve. This stimulation is accompanied by increased stickiness and permeability of the endothelium.

Pitressin (beta hypophamine), if injected into dogs, produces pressor effects by causing contraction of small arterioles and probably of capillaries. Macroscopically one finds on the valves (usually the mitral) of animals killed an hour to three days after injection of pitressin small flat lesions of cherry color.

More striking are the microscopic changes in the valvular endothelium. The latter swells, its nuclei become shorter and thicker, later, oval and round, and finally the cells again appear elongated but perpendicular to the surface of the valve. The swelling of the cytoplasm continues to such an extent that in some places the endothelium protrudes from the surface of the valve into the cavity

of the heart. The cytoplasm appears gelatinous and stains poorly. Gelatinous expansions of the endothelial cytoplasm in many places are seen far above the surface of the valve, projecting freely into the cavity of the heart. Occasionally, these expansions, leaflet-like and stringy, are so long that they may be mistaken for adherent fibrin or platelet material. In some instances a group of endothelial cells can be seen multiplied and swollen to the point of forming a patch on the surface.

If bacteria are introduced into the blood stream after injection of pitressin and the animals are killed at intervals of from one day to twenty-three days the pathologic changes in the mitral valve can be observed macroscopically, ranging from a pinpoint-sized lesion to an ulcerative endocarditis. Microscopically there is a gradual settling and invasion of the surface of the valve by the bacteria. Finally, the endothelium, filled with bacteria, becomes necrotic and falls off, leaving the surface of the valve denuded.

In some experiments repeated injections of pitressin alone lead to true bacterial endocarditis, the bacteria (in my case, cocci) being of endogenous origin. This is to be expected since the pressor episodes influence the endothelium of the whole body, including that of the respiratory tract, causing it to become permeable and permitting bacteria to invade the blood stream.

These observations should explain the mechanism of the development of bacterial endocarditis.

The endothelium of the valves attracts the bacteria floating in the blood because it has become sticky and permeable, holding the bacteria and offering them an opportunity for invasion and multiplication.

DISCUSSION

PAUL CANNON: What happens to endothelial cells in tissues such as the ovary, the kidneys, the spleen and heart valves other than the mitral when pitressin is injected?

O. SAPHIR: These experiments with pitressin are interesting, but in the illustrations I did not see true endocarditis except perhaps in one. Were these acute verrucous lesions?

R. KRONFELD: When teeth like those I have shown are extracted the bacteria are on the surface, not in the tissues. When the tissues are traumatized bacteria may penetrate. Was the epicardium examined and were the lesions obtained with pitressin on the ventricular or on the auricular surfaces of the cardiac valves?

S. A. LEVINSON: Were bacteriologic studies made of the valves? Pilot and David have found that a large percentage of the tonsils in dogs harbor hemolytic streptococci.

A. J. NEDZEL: The endothelium in other organs was not studied and that in the heart was examined only when gross changes were noted. The lesions obtained with pitressin appeared on both the auricular and the ventricular surface of the valves.

F. B. MOOREHEAD: I have observed several patients acquire acute endocarditis following extraction of teeth, but I have not associated seasonal or climatic changes with this infection. I believe that curetting or traumatizing infected peridental tissues is dangerous, just as with tonsillectomy.

CYSTIC TUMOR OF THE THIRD VENTRICLE WITH COLLOID-LIKE CONTENT. HOWARD ZEITLIN and BEN LICHTENSTEIN.

Two cases of cystic tumor with colloid-like content arising from the most rostral end of the roof of the third ventricle are reported. One occurred in a white woman of 46 years who had complained of attacks of headache for more than twelve years. At first the headaches were associated with epileptiform seizures, but during

the last two years of her illness hypersomnolence was the outstanding clinical manifestation. The second case occurred in an adult white man who had had headaches for five years. The last attack was sudden and was associated with vomiting and later with hypersomnolence.

Each brain had a markedly dilated third ventricle occupied by a large cystic tumor. The floor of the third ventricle and the hypothalamic nuclei were compressed. Each cystic tumor had a connective tissue capsule lined by a layer of epithelial cells. Both cysts contained a thick gelatinous material. The connective tissue capsules had many tubules lined by similar cells. On the innermost aspect of the swollen epithelial cells lining the cysts were small groups of bulging spherical globules that frequently had the appearance of secretory function. The tubules in general were similar to those described in the paraphysis of the human embryo and lower vertebrates.

These data and the classic position of each of these cysts, at the roof of the third ventricle, substantiate the theory that such cysts are derivatives of the embryonic structures of the paraphysis.

It is suggested that the cystic tumors which have been described as colloid-like and the neuro-epithelial cysts of the third ventricle be named paraphysial.

The complete report will be published in the *Archives of Neurology and Psychiatry*.

DISCUSSION

G. B. HASSIN: This study reveals the ontogenetic origin of the cysts of the third ventricle.

BEN W. LICHTENSTEIN: The clinical symptoms in such cases are variable. Sometimes the cyst causes epileptiform seizures, sudden death, etc. In every case it seems to impinge on the hypothalamic nuclei in the floor of the third ventricle.

Book Reviews

666 Pathology of the Nervous System. A Student's Introduction. By J. Henry Biggart, M.D. (Belfast), Pathologist to the Scottish Asylums' Board; Neuropathologist to the Royal Infirmary, Edinburgh; Lecturer in Neuropathology, Edinburgh University; some time Commonwealth Fellow in Pathology, Johns Hopkins University, Baltimore. Foreword by Professor A. Murray Drennan, M.D., F.R.C.P. Price, $5.25. Cloth. Pp. 335, with 204 illustrations. Baltimore: William Wood & Company, 1936.

This book has grown out of lectures to medical students and to candidates for a special diploma in psychiatry. Its purpose is to "help the student to apply the general principles of pathology, which he has already learnt in his study of the disease process in other organs, to the lesions of the nervous system." The first three chapters deal with the neuron, the interstitial cells of the nervous system and the cerebrospinal fluid in their relations to disease. The morphologic changes of the cells of nervous tissue are described well and clearly. Then come chapters on vascular and infectious diseases, including those in which viruses have been shown to be the causative factors. On page 147 Leilie should be Lillie. Under diseases of unknown etiology, but possibly infective, are included acute perivascular myelinoclasis in smallpox, chickenpox, measles and vaccinia; disseminated sclerosis; neuromyelitis optica and diffuse cerebral sclerosis. The chapter on intoxications and deficiency diseases includes chorea, toxic myelitis, neuritis of bacteriotoxic origin including tetanus, lead and arsenic poisoning, chronic alcoholism, carbon monoxide poisoning, pregnancy toxemia, hepaticolenticular degeneration, ergotism, pellagra, beri-beri and pernicious anemia. In the discussion of the genesis of tetanus no attention is paid to the recent work of Abel and his associates on the absorption and distribution of tetanus toxin by way of the blood, which has opened up again the question of the ascension of the toxin by way of the nerves. Under degenerative diseases are discussed senile dementia, paralysis agitans, Huntington's chorea, amaurotic family idiocy, syringomyelia, the hereditary ataxias, amyotrophic lateral sclerosis, the muscular atrophies, myotonia congenita and atrophica, myasthenia gravis. Is the last disease bacterial in origin? A good summary is given of the immediate and remote structural changes caused by injuries to the nervous tissues. Tumors of the nervous system are presented in two well organized chapters; the gliomas are grouped according to the classification by Bailey and Cushing, as modified by Cox. The final chapter deals with errors of development (cerebral diplegia and hemiplegia, porencephaly, spina bifida and tuberous sclerosis). The book describes well in clear and direct style the morphologic processes in the diseases of the nervous system indicated in the foregoing. The descriptions are aided greatly by the uniformly good illustrations, all original, of gross and microscopic appearances, the latter as revealed by general as well as special (Nissl, Cajal, Hortega) methods. At the end of each chapter are a few references to papers in English, mostly monographs, in order to encourage further reading. The book is recommended as a highly useful introductory guide to the study of neuropathology in its relations to the pathology of other systems.

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